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The journal has a goal of serving as an important resource material in diabetes for its readers, mainly in the developing world.

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EDITORIAL

Diabetes and metabolic dysfunction-associated steatotic liver disease, CVD: a continuum

Rajeev Chawla[1] · **Anshul Kumar**[2]

Published online: 31 July 2024

Non-alcoholic fatty liver disease (NAFLD) has emerged as the predominant chronic liver condition worldwide, affecting an estimated 38% of the global adult population [1]. Regional prevalence varies significantly, with lower rates observed in Africa (13.5%) and higher rates in regions such as Mexico, Central and South America, the Middle East, and South Asia, where prevalence exceeds 30% [2, 3]. However, these figures may underestimate the true scope of the disease.

Underdiagnosis of NAFLD remains a significant barrier to effective medical management, complicating efforts to gauge disease prevalence and associated complications. Factors contributing to underdiagnosis include limited awareness among both patients and healthcare providers, the typically asymptomatic nature of NAFLD in its early stages, and the lack of standardized diagnostic tools. Although plasma aminotransferase levels and liver ultrasonography are commonly used screening methods, their sensitivity in diagnosing and monitoring NAFLD is limited.

In 2023, three major international liver associations proposed replacing the term NAFLD with metabolic dysfunction-associated steatotic liver disease (MASLD), and non-alcoholic steatohepatitis (NASH) with metabolic dysfunction-associated steatohepatitis (MASH). Current epidemiological data suggest a high concordance rate between NAFLD and MASLD definitions, with approximately 99% overlap [4].

MASLD is a multisystem disorder in which systemic insulin resistance and related metabolic dysfunctions contribute to its development and associated liver-related morbidities (cirrhosis, liver failure, hepatocellular carcinoma) and extrahepatic complications, including cardiovascular disease (CVD), type 2 diabetes mellitus, chronic kidney disease, and certain cancers. MASLD is closely linked with visceral adiposity, atherogenic dyslipidaemia (low HDL cholesterol, elevated triglycerides/remnant lipoproteins, small dense LDL), and insulin resistance with or without hyperglycaemia. Importantly, MASLD confers a cardiovascular risk greater than the sum of its individual comorbidities [5].

MASLD is recognized as a significant risk factor for major adverse cardiovascular events, the leading cause of mortality among affected adults [6, 7]. Recent meta-analyses underscore the elevated risk of all-cause mortality, cardiac-specific mortality, and specific cancer-related mortality associated with MASLD [6].

Furthermore, MASLD increases the risk of developing CVD outcomes independent of traditional cardiometabolic risk factors, with higher incidence rates observed in cases of non-cirrhotic fibrosis and cirrhosis [7].

MASH affects approximately 20% of MASLD patients, characterized by chronic liver inflammation and systemic inflammation. The aetiology of this inflammation is multifaceted, involving various proinflammatory cascades and cytokines, including NLRP3 inflammasomes [8, 9]. Chronic liver inflammation drives liver fibrosis and complicates MASLD outcomes, while systemic inflammation contributes to CVD and oncogenesis.

The study by Prashasti Gupta and Aparna Agrawal [10] "Correlation of presence and severity of glucose derangements with severity of liver cirrhosis: a hospital-based cross sectional observational study from New Delhi" has been carried out with the aim of studying the correlation between GMD (glucose metabolism disorder) and the severity of LC (liver cirrhosis) as determined by the Child-Turcotte-Pugh (CTP) score. Out of 100 patients, 6, 21, and 73 were respectively found as falling under CTP class A, B, and C of LC. The frequency of diabetes mellitus (DM) was found to progressively increase with a worsening grade of cirrhosis (17%, A; 24%, B; and 27%, C). However, this study concluded that the development of GMD and IR (Insulin resistance) may be independent of the severity of LC.

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The study by Danting Li [11] from Sichuan University, China, published in the present issue "Correlation between triglyceride-glucose index and related parameters and non-alcoholic fatty liver disease in northwest China" has highlighted that triglyceride glucose (TyG) index and obesity are significantly closely related to the incidence of nonalcoholic fatty liver disease (NAFLD). The study aimed to investigate the relationship between the TyG index and its related parameters [TyGwaist circumference (WC) and TyG-body mass index (BMI)] with NAFLD.

Given that MASLD significantly elevates CVD morbidity and mortality, it is crucial to mitigate these risks. Patients with MASLD present a heterogeneous array of CVD risk factors, necessitating personalized treatment strategies tailored to individual risk profiles based on age, sex, ethnicity, and geographic location. Accurate assessment of CVD risk using region-specific calculators is therefore essential in managing MASLD effectively.

In conclusion, identifying MASLD is pivotal for CVD prevention and treatment, highlighting the need for heightened awareness among healthcare providers.

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REVIEW ARTICLE

Global trend of research and publications in endocrinology, diabetes, and metabolism: 1996–2021

Raju Vaishya[1] · Anoop Misra[1,2] · Mahmoud Nassar[1,3] · Abhishek Vaish[1,4]

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Abstract

Background & Aims Diabetes and related metabolic syndromes represent a significant global health challenge, with the global burden of diabetes increasing considerably since 1990. In this article, we examined the trend of publications in Endocrinology, Diabetes and Metabolism between 1996 and 2021, focusing on Asian countries.

Methods We obtained and used the data from the Scopus database from the SCImago website (https://www.scimagojr.com/), on 1 April 2023, related to the subspecialty of Endocrinology, Diabetes and Metabolism for country rankings between 1996 and 2021. We did not include any data related to other medical specialties or other fields.

Results There has been a steady rise in global publications on these subspecialties over the past decade, with the number of publications from Asian countries increasing significantly. Western Europe recorded the highest number of publications, followed by North America and Asia. The COVID-19 pandemic also contributed to a surge in publications in this field. In Asian countries, China and India have notably increased their global contribution to publications, with China emerging as the top Asian nation in 2021.

Conclusion Our findings provide valuable insights into the research output from various countries and the productivity trends in Diabetes, Endocrinology and Metabolism-related research.

Keywords Diabetes · Endocrinology · Metabolism · Publications · Asian countries

Introduction

Diabetes and related metabolic syndromes represent a significant global health challenge in recent times. The global burden of diabetes has increased considerably since 1990, with substantial variations observed across regions and countries [1]. According to the World Health Organization (WHO), the prevalence of diabetes has risen almost fourfold, from 108 million in 1980 to 422 million in 2014, with an associated 3% increase in diabetes-related deaths between 2000 and 2019 [2]. The International Diabetes Federation (IDF) estimated that the global prevalence of diabetes was 9.3% in 2019, projected to increase to 10.2% in 2030 and 10.9% in 2045. Diabetes is more prevalent in high-income countries (HIC) (10.4%) than in low-and-middle-income (LMIC) countries (4.0%) and in urban areas than in rural areas [3]. It is concerning that the prevalence of diabetes is rising more rapidly in LMIC countries than in HIC countries, necessitating urgent public health and clinical preventive measures [1, 2, 4]. In particular, China and India have the largest number of people with diabetes globally, and occupy number one and number two positions, respectively [5, 6]

To contribute to understanding the global research publication trend in Endocrinology, Diabetes and Metabolism, we aimed to investigate the trend of publications between 1996 and 2021 using Scopus data on the SCImago Journal and Country Rank (SJR) website. Specifically, we sought to compare the trend of global publications by Asian countries.

Highlights
- Global publications on diabetes and associated diseases have steadily risen
- Asian countries, particularly China and India, have shown a good growth
- COVID-19 pandemic led to a surge in publications, with highest from Western Europe

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Materials and methods

The data for this study were obtained from the SCImago website (https://www.scimagojr.com/), on 1 April 2023, by the lead author (RV) of this study. Specifically, we searched for data related to the subspecialty of Endocrinology, Diabetes and Metabolism for country rankings between 1996 and 2021. The following search strategy was used: SCImago website >> Country Ranking >> All subject areas >> Endocrinology, Diabetes and Metabolism >> All regions > Asian regions >> 1996–2021. For this review, we only included the data related to the specialty of Endocrinology, Diabetes and Metabolism and did not include any data related to other medical specialties or other fields. The data were downloaded and recorded in Excel spreadsheets for further analysis. We evaluated the data of all countries, focusing on Asian countries.

The SCImago Journal & Country Rank (SJCR) provides a publicly available and freely accessible platform for determining the ranking of scientific journals and countries. SJCR utilizes scientific indicators developed from the Scopus database, managed by international publisher Elsevier B.V. and updated annually. The rankings of journals, countries and regions can be analysed and compared using these indicators. Additionally, journals can be grouped according to the subject area and category or by country. As such, SJCR provides researchers with a valuable tool for drawing important metrics on journals [7].

Results

Over the past 25 years (1996–2021), 576,722 publications were recorded in Endocrinology, Diabetes and Metabolism, originating from 216 countries. The number of publications in 2021 was 43,960, representing an increase from the yearly average of the previous 25 years, which was 23,068.9. Notably, the number of publications in these subspecialties has steadily risen globally over the past decade, increasing from 26,328 in 2012 to 43,960 in 2021 (Fig. 1).

A total of 89,312 articles related to the subspecialty of Endocrinology, Diabetes and Metabolism were published by 32 Asian countries between 1996 and 2021, with an average of 3572.5 articles per year. Notably, publications from Asian countries increased significantly in 2021, with 10,541 articles published. In recent years, there has been a substantial rise in publications from Asian countries, with an increase from 4070 publications in 2012 to 10,541 publications in 2021 (Fig. 2).

The percentage of global publications originating from Asian countries has demonstrated a consistently increasing trend over the past decade. From 2012 to 2021, the percentage of publications increased from 15.49% to 23.98%. Notably, several Asian countries have improved their ranking in 2021, except Japan, which experienced a decline in rank from 5 to 6 (Supplement 1).

China has demonstrated significant improvement in its global ranking, emerging as the top Asian nation in 2021 with a global rank of 2 compared to an average yearly rank of 6 over the past 25 years. Furthermore, China's rank amongst Asian countries reached number 1 in 2021 and is way ahead of its other regional neighbours with regard to the quantum of publications. The country's contribution to global publications has increased substantially in the past decade, rising from 4.47% in 2012 to 11.85% in 2021, representing a 165.1% increase. Similarly, India has notably increased its global contribution from 1.55% in 2012 to 2.59% in 2021, signifying a 67% rise (Fig. 3).

India has demonstrated a notable positive trend in publications related to Endocrinology, Diabetes and Metabolism. India's global ranking in this field improved significantly in 2021, with a rank of 10, in contrast to an average yearly rank of 16 over the past 25 years. Amongst Asian countries, India currently ranks third, following China and Japan (Table 1).

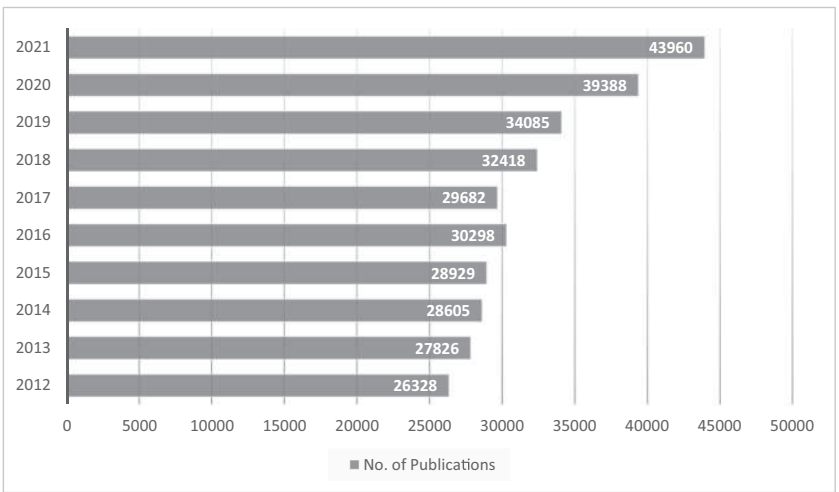

Fig. 1 Global trends of publications in Endocrinology, Diabetes and Metabolism, 2011–2021

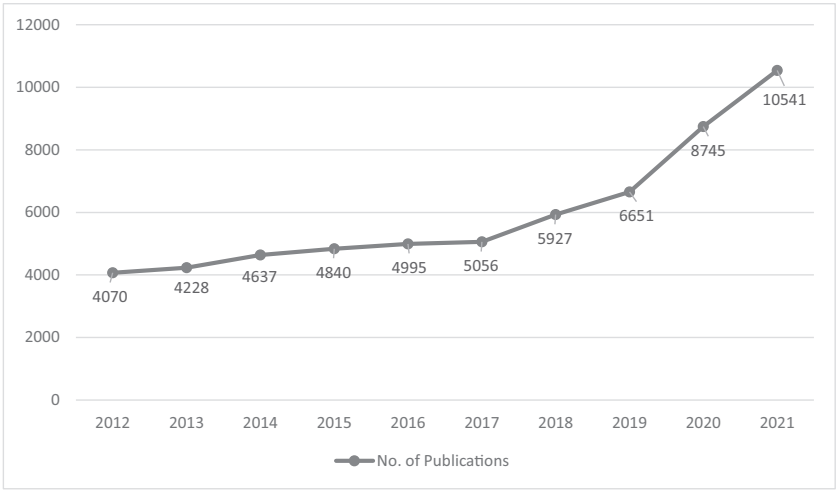

Fig. 2 Trend of publications in Endocrinology, Diabetes and Metabolism amongst Asian countries between 2012 and 2021, showing 158.75% growth

Table 1 provides various metrics related to publications by the 30 listed Asian countries between 1996 and 2021 [7]. It is interesting to note that between the cumulative period from 1996 to 2021 (Table 2), Japan had the maximum number of publications (28,609), followed by China (27,103) and India (9531). However, in 2021 (Table 1), China led the publication list significantly, with 5703 yearly publications, followed by Japan (1490) and India (1097).

Global countries with the highest volume of publications, and their trends in Endocrinology, Diabetes and Metabolism over the past three years, are presented in Fig. 4. Developed countries are prominent in this list, except India, a developing nation that made the list of top 10 countries in 2021 but is still considerably behind the USA and European countries. The United States remained the leading country, followed by China and the United Kingdom (Supplement 2).

The highest number of publications related to Endocrinology, Diabetes and Metabolism between 1996 and 2021 (see Fig. 4) was reported from Western Europe, with 227,560 publications, followed by North America, with 153,436 publications, and Asia, with 89,312 publications. Conversely, Africa was the least productive region, with only 6179 publications in this field. Table 2 lists the top three countries in each of these regions.

Endocrinology, Diabetes and Metabolism witnessed a significant increase in global publications during the initial phase of the COVID-19 pandemic from 2020 to 2021. This trend was also observed in other medical specialties. Kambhampati et al. attributed the surge in publications during the pandemic to various factors, such as increased availability of time for authors to publish, ease of publishing as most journals actively sought COVID-19-related articles, and the fast-tracking of the editorial and publishing processes [8].

Discussion

In this study, we present valuable insights into the trends of publications related to Endocrinology, Diabetes and Metabolism over the past 25 years globally. The study had several strengths,

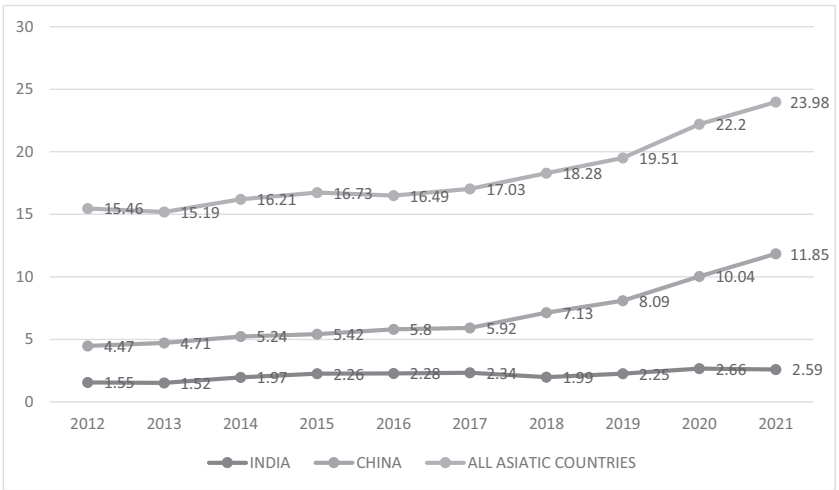

Fig. 3 Percentage contribution of all Asian countries, China and India to the Global research publications on Endocrinology, Diabetes and Metabolism during 2012–2021

Table 1 Publication metrics of Asian countries in 2021, with China ranking at number 1 (Source: SCImago [7])

Rank	Country	Documents	Citations	Citations per document	H Index
1	China	5703	22183	3.89	187
2	Japan	1490	5891	3.95	252
3	India	1097	5587	5.09	153
4	South Korea	843	3756	4.46	166
5	Taiwan	371	1844	4.97	123
6	Singapore	254	1549	6.1	122
7	Hong Kong	211	1411	6.69	121
8	Malaysia	179	652	3.64	66
9	Thailand	168	701	4.17	74
10	Indonesia	142	820	5.77	48
11	Pakistan	132	687	5.2	70
12	Bangladesh	81	323	3.99	48
13	Viet Nam	61	288	4.72	35
14	Philippines	53	287	5.42	42
15	Sri Lanka	41	132	3.22	36
16	Nepal	30	154	5.13	25
17	Kazakhstan	21	93	4.43	17
18	Macao	7	61	8.71	25
19	Kyrgyzstan	7	79	11.29	9
20	Tajikistan	6	70	11.67	7
21	Turkmenistan	6	70	11.67	6
22	Afghanistan	4	13	3.25	7
23	Brunei Darussalam	3	3	1	9
24	Laos	2	7	3.5	6
25	Myanmar	2	1	0.5	6
26	Bhutan	1	1	1	1
27	Uzbekistan	1	10	10	8
28	Cambodia	1	0	0	8
29	Mongolia	1	2	2	13
30	Maldives	1	0	0	6

Table 2 Regional contribution of publications and the top three prolific countries in each region during 1996–2021

	Region	Country	Publications number
1	Western Europe	United Kingdom	43,136
		Italy	35,132
		Germany	31,000
2	North America	United States of America	153,436
		Canada	21,225
3	Asian Countries	Japan	28,609
		China	27,103
		India	9531
4	Eastern Europe	Poland	10,246
		Russian Federation	5075
		Czech Republic	4097
5	Middle East	Turkey	8500
		Iran	6545
		Israel	5241
6	Latin America	Brazil	12,079
		Argentina	3322
		Mexico	2782
7	Pacific	Australia	17,523
		New Zealand	2808
		Fiji	36
8	Africa	South Africa	1807
		Nigeria	687
		Tunisia	626

Egypt (publication number 2051) was included in both Middle East and African countries, and hence it was removed from the list of Africa to avoid duplicity)

such as using a robust data source (Scopus) and using the SJCR platform to determine the ranking of scientific journals and countries. The study focused on Asian countries, which highlighted the growing role of these countries in contributing to the global knowledge base of diabetes research. Such an analysis has not been previously done, to the best of our knowledge.

Overall, the global burden of diabetes has increased significantly since 1990, and it varies substantially across regions and countries [1, 3, 9]. The trend of the global prevalence of type 2 diabetes (T2D) is similar to that of the total burden of diabetes, including people with both T2D and type 1 diabetes (T1D). While the global age-standardized mortality rate and disability-adjusted life years (DALYs) for T1D have declined, an increase in the incidence of T1D is expected by 2040, with the largest relative increase projected to occur in LMIC [4]. An increase in risk factors, including excess BMI, inappropriate diet, low physical activity and smoking, contribute to most attributable deaths and DALYs related to T2D [1].

The IDF Diabetes Atlas (10th edition) reported a continued global increase in diabetes prevalence, confirming it to be a significant global health challenge. In 2021, there were 537 million adults living with diabetes, and this figure is predicted to rise substantially to 643 million by 2030 and 783 million by 2045. Furthermore, it is disturbing that over 3 in 4 adults with diabetes live in LMIC. In addition, diabetes was also responsible for 6.7 million deaths in 2021 [9].

Numerous research studies have been conducted on diabetes in various countries and regions, with differing output and quality levels. For instance, a scientometric analysis of Indian authors using Web of Science (WOS) data from 1989 to 2021 reported that India ranked ninth globally in terms of diabetes research output in 2019, with only 2.23% of the publications being highly cited [10]. Similarly, a bibliometric

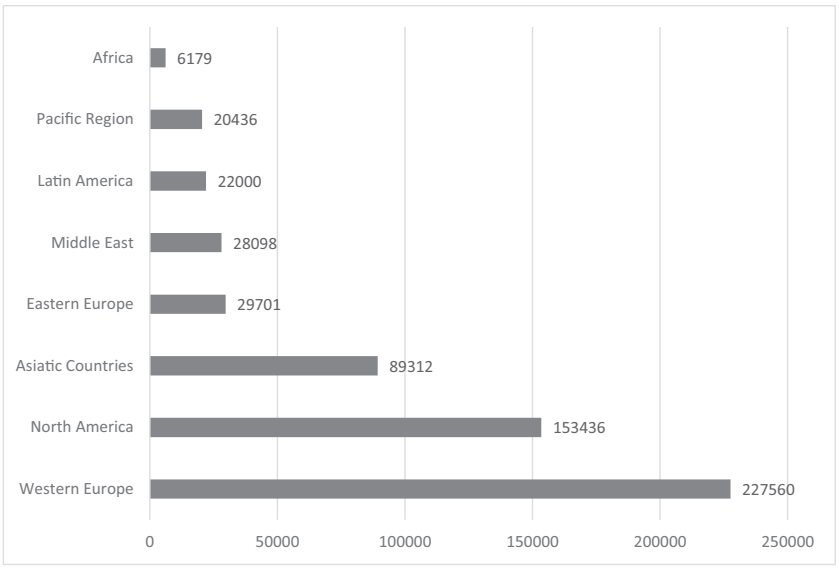

Fig. 4 Number of publications in different world regions from 1996 to 2021 (The X-axis shows the number of publications, and the Y-axis denotes the region)

study analysing T2D-related research from the Scopus database between 1982 and 2019 found that the productivity of diabetes research in India lags behind, highlighting the need for increasing internal funding for research, national and international collaborations, active involvement of national and international funding agencies, and prioritizing research on youth with T2D [11]. Data from other regions also show encouraging trends. A scientometric analysis conducted in the Middle East shows an overall increasing trend of publications on diabetes from the region [12–14].

We believe that the probable reasons for the growth of publications from China and India are the increasing numbers of people with diabetes in these regions, more awareness amongst researchers to address their local problem of diabetes, and its relationship with changing diet and lifestyle [15, 16], COVID-19 [17] and tuberculosis syndemic [18]; in addition to the establishment of more high-end academic medical institutions in several cities of India, better research funding available, etc. [19].

This study has several strengths. Firstly, we used a robust data source (Scopus) to investigate the global trend in publications, which is the world's largest abstract and citation database of peer-reviewed literature. Using such a comprehensive database enabled us to draw more reliable conclusions. Secondly, the study was focused on Asian countries and other geographical regions, and with the help of data, it is possible to uncover important regional patterns and nuances, which could inform targeted interventions and policymaking. Lastly, we utilized the SJCR platform to determine the ranking of scientific journals and countries, enabling researchers to draw important metrics on journals and countries. This provided a comprehensive way to compare the productivity of different countries and journals, allowing researchers to identify areas of excellence and opportunities for improvement.

While this study has many strengths, there are also some limitations. Firstly, we investigated the trend of publications without examining the quality or impact of the publications. Without evaluating the quality of the publications, the study's findings may not accurately reflect the usefulness of the research. Secondly, the study was limited to the data available on Scopus and SJCR, which may not be comprehensive. For example, publications in non-English languages or non-indexed journals could not be included. This may have led to a potential underrepresentation of research output in some countries and regions. Lastly, we did not analyse the factors contributing to the increase in publications or the differences in diabetes research output between countries, which could limit the generalizability of the findings.

This study highlights the need for continued research and development in the field of diabetes and related metabolic syndromes, particularly in LMIC countries, where the prevalence of diabetes is rising more rapidly than in HIC countries. Since there has been an increasing trend of Diabetes and Metabolic disorders in the LMICs such as India, more research is needed [15] from these areas to address their unique problems and their remedies, as the research outputs from HIC may not be appropriate to apply in the management of problems in LMIC populations. All associated risk factors and consequences of diabetes need more investigation [15]. Therefore, more international collaboration and research funding are required for the researchers of LMIC [20, 21].

Conclusion

This study provides valuable insights into the global trend of publications and demonstrates a significant increase in the specialty of Endocrinology, Diabetes and Metabolism over the past decade, with Asian countries showing a substantial rise in productivity. China and India, in particular, have exhibited notable improvement in their global contribution and ranking, signifying the growing importance of these countries in the field. Overall, this study contributes to understanding the global landscape of Endocrinology, Diabetes and Metabolism research, providing valuable information for researchers, practitioners and policymakers alike.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13410-023-01221-4.

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Data availability All the raw data is available from the authors and can be provided, if need be.

Ethical approval Not required.

Use of LLMs/AI technology None

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REVIEW ARTICLE

Effects of novel glucose-lowering drugs on the COVID-19 patients with diabetes: A network meta-analysis of clinical outcomes

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Abstract

Objective This study aimed to assess the effects of sodium-glucose co-transporter inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1RA), and dipeptidyl peptidase-4 inhibitors (DPP4i) on individuals subjected to diabetes and COVID-19.

Methods PubMed, Embase, Web of Science, and Cochrane Library were systematically searched to cover studies (except for case reports and review studies) published until August 30, 2022. The primary outcome was the mortality of people with diabetes and COVID-19. The secondary outcomes comprised the requiring intensive care unit (ICU) admission and mechanical ventilation. Two reviewers independently screened studies, abstracted data, and assessed risk-of-bias. Furthermore, the network meta-analyses (NMA) were conducted.

Results A total of 12 trials were involved in the analysis. The OR and 95% CI of mortality for SGLT2i compared with SGLT2i + GLP-1RA and DPP4i reached 0.41 (0.17,0.97) and 0.69 (0.49,0.98), respectively. The OR and 95% CI of requiring mechanical ventilation for SGLT2i compared with the DPP4i reached 0.85 (0.75,0.97).

Conclusions As revealed by the result of this study, SGLT2i is associated with the lower mortality rate in people with diabetes and COVID-19 among novel glucose-lowering drugs. And SGLT2i is linked to lower requiring mechanical ventilation. These findings can have a large impact on clinicians' decisions amid the COVID-19 pandemic.

Keywords COVID-19 · Diabetes · SGLT2 inhibitors · GLP-1 agonist · DPP-4 inhibitors

Introduction

Since the end of 2019, SARS-CoV-2 has emerged as a novel disease-causing microorganism leading to the COVID-19 pandemic. By the end of October 2022, more than 622 million people had been infected with SARS-CoV-2 globally, approximately 6 million of whom died [1]. The COVID-19 pandemic was superimposed on the pre-existing diabetes pandemic, creating a large population of people with diabetes and COVID-19.

Existing research has suggested that diabetes is an independent risk factor for worse outcomes and in-hospital mortality in COVID-19 patients [2–5]. In addition, other co-morbidities common to patients with diabetes, such as cardiovascular disease (CVD) and obesity, put COVID-19 patients at greater risk of poor clinical outcomes [6, 7]. Chronic hyperglycemia can impair innate and humoral immunity. In addition, diabetes is correlated with chronic, low-grade inflammatory states that affect glucose regulation and peripheral insulin sensitivity [8]. There is a two-way correlation between COVID-19 and diabetes. Diabetics are at an increased risk of complications when infected with COVID-19; besides, SARS-CoV-2 may serve as a diabetic agent by binding to ACE2 in pancreatic β cells, thus resulting in acute dysfunction and altered glucose regulation [9]. All approved oral antidiabetic agents can be safe in T2DM patients and COVID-19 [10], whereas no conclusive data have been available to indicate a mortality benefit with any class of the above-mentioned drugs in the absence of large randomized controlled trials. However, the metabolic management of patients should be optimized to improve outcomes and reduce the burden on health systems.

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Whether commonly used glucose-lowering agents in diabetes patients affect COVID-19 patient prognosis should be determined since the mechanism of action of glucose-lowering drugs may affect the natural course of SARS-CoV-2 infection. Moreover, insights should be gained into whether the above-described drugs are harmful, neutral, or beneficial for COVID-19 patients. Besides, a relatively beneficial treatment option should be urgently selected from the many available for people with diabetes and COVID-19. Existing research has reported that antidiabetic drugs exert antidiabetic effects and anti-inflammatory and immunomodulatory effects [2, 11]. Numerous studies have investigated the effects of antidiabetic drugs on the clinical outcomes of COVID-19 diabetes patients. Several paired meta-analyses have examined the effects of specific antidiabetic agents on COVID-19 mortality and serious adverse outcomes, which comprise metformin, dipeptidyl peptidase 4 inhibitors (DPP4i), sulfonylureas, as well as insulin and glucagon-like peptide-1 receptor agonists (GLP-1RA) [11–13]. However, the above-mentioned studies only compared patients who used specific antidiabetic drugs with non-users. The risk of death between different antidiabetic drugs in the above-described patients remains unclear.

Sodium-glucose co-transporter inhibitors (SGLT2i), GLP-1RA, and DPP4i have been confirmed as novel glucose-lowering agents for the management of diabetes [14]. Novel glucose-lowering medications may reduce adverse COVID-19 outcomes for their anti-inflammatory properties, whereas rare research has systematically investigated the potential role of different pharmacological classes in adverse COVID-19 outcomes thus far [15]. Previous research has reported that DPP4i plays a beneficial role in T2DM patients hospitalized for COVID-19 [15, 16]. SGLT2i and GLP-1RA exhibit several anti-inflammatory properties, which may be correlated with better outcomes [15, 17]. In contrast, safety concerns have been raised for SGLT2i and GLP-1RA since they up-regulate ACE2 expression, such that SARS-CoV-2 binding to the cells is mediated [18]. However, RAAS inhibitor drugs, which also up-regulate ACE2 expression, do not appear to be correlated with an increased risk of incident COVID-19 or worse outcomes in prevalent COVID-19 [19]. There are no independent studies assessing the effects of the three novel hypoglycemic agents in people with diabetes and COVID-19. Accordingly, no clear consensus has been reached on using the above three agents in the above-mentioned patients. On that basis, this knowledge gap was filled through network meta-analyses (NMA) and the assessment of three novel glucose-lowering drugs (i.e., SGLT2i, GLP-1RA, and DPP4i) on mortality and morbidity of severe disease in people with diabetes and COVID-19. Mortality in people with diabetes and COVID-19 served as the primary outcome. In terms of the secondary outcome of this study, the incidence of severe disease (requiring intensive care unit admission; mechanical ventilation) in people with diabetes and COVID-19 was also assessed.

Methods

The PROSPERO registration number was CRD42022355190. Our meta-analysis was consistent with the PRISMA statement and also the network meta-analysis extension statement of PRISMA (Sup. Table 1).

Searching strategy

PubMed, Embase, Web of Science, and Cochrane Library were systematically searched for relevant studies up to August 30, 2022, and our search was limited to the English language. Search terms comprised novel glucose-lowering drugs (e.g., SGLT2i, GLP-1RA, and DPP4i), diabetes, and COVID-19. The detailed and complete search strategy is presented in Sup. Table 2. Imported the retrieved studies into EndnoteX9 and extracted them by filtering their titles and abstracts. Duplicate studies and multiple reports using the same data were removed. After initial screening, ineligible studies were excluded by reading the complete text, and the final remaining studies were covered.

Inclusion criteria

Study type that conformed to the requirements of the non-randomized trials and observational studies. The study subjects were adults (aged ≥ 18 years) with diabetic COVID-19. Intervention measures are novel glucose-lowering drugs (e.g., SGLT2i, GLP-1RA, and DPP4i). All the covered literature should report any one of the primary or secondary outcome indicators, the primary outcome was the mortality of people with diabetes and COVID-19, and the secondary outcomes were the requiring intensive care unit (ICU) admission and mechanical ventilation. Studies published in English were searched.

Exclusion criteria

Exclusion criteria are presented as follows: case reports, review studies and abstracts, duplicate publications in the literature, literature for which complete data could not be extracted, animal studies, non-adult patient, and non-English language studies.

Data extraction

The relevant data were extracted by two independent evaluators (Y Y, LZ) using a predetermined data collection form following the inclusion criteria. The primary data extracted comprised study characteristics (e.g., first author, publication date, country, and study design), characteristics of the patient (e.g., sample size, mean age,

and proportion of males), as well as study outcome data. Any disagreements in the data extraction process would be resolved through discussions with a third reviewer (CL).

Risk of bias assessment

The risk of bias assessment was conducted by two independent authors using the Newcastle–Ottawa Scale (NOS) [20]. Any disagreements during the risk of bias assessment would be resolved by discussion.

Statistical analysis

The ratio (OR) and 95% confidence interval served as the effect size indicators for the dichotomous variables (e.g., mortality, requiring intensive care unit admission, and mechanical ventilation). The heterogeneity between studies was estimated through the I^2 test. After the exclusion of effects exerted by significant clinical heterogeneity, the random-effects model was employed for the meta-analysis. The network meta-analyses (NMA) were conducted using STATA 16.0 software based on a frequency-based random effects model, in which the study outcome measures were networked by the group command. Data processing, network evidence plots, funnel plots, forest plots, and surface area under the cumulative rankograms (SUCRA) were completed sequentially. The area enclosed by the curve and the horizontal axis in the SUCRA plot can indicate the percentage of treatment effectiveness (SUCRA value), which is ranked without any uncertainty. The ranking of the treatment modality will be improved with the rise of the SUCRA value. Publication bias of the relevant literature was assessed using funnel plots. $P<0.05$ indicated a difference that achieved statistical significance.

Results

Literature search and screening

In this study, 378 studies were initially searched. 12 studies were finally covered after a hierarchical screening process. Figure 1 illustrates the selection of the literature.

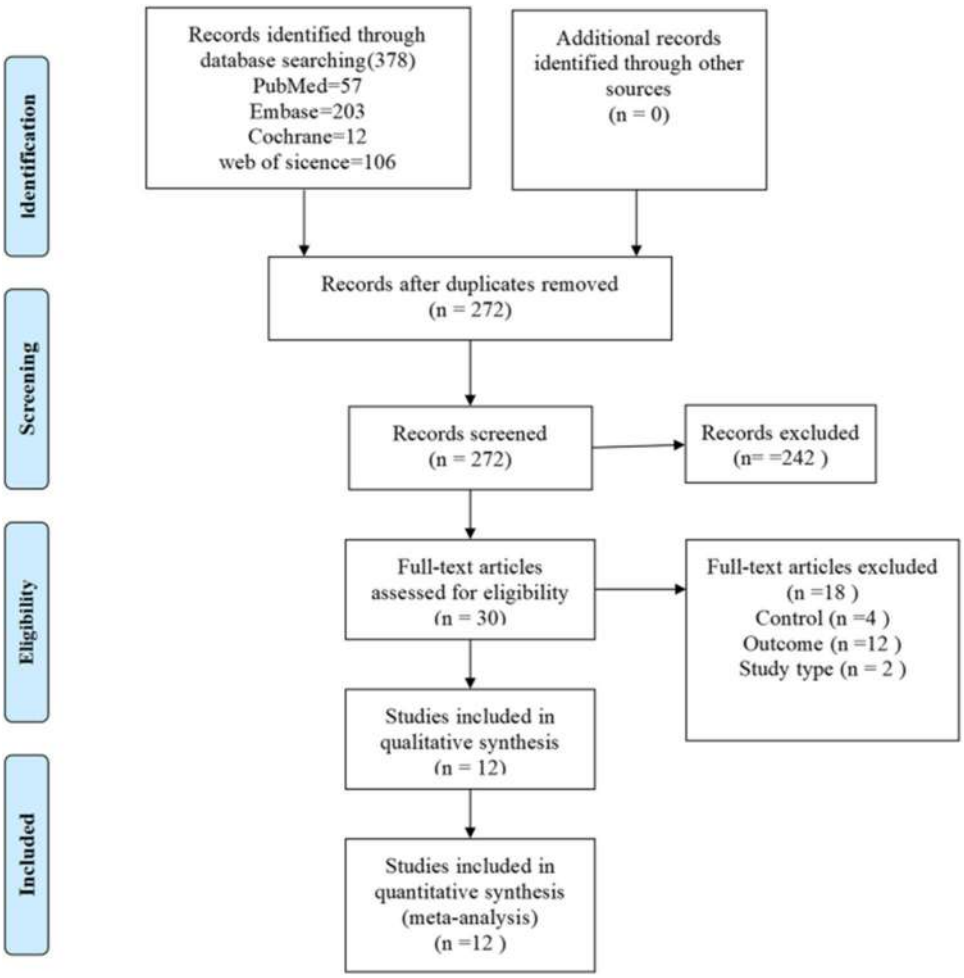

Fig. 1 The flow diagram of study selection

Basic characteristics of involved literature

A total of 12 studies were covered in the literature [21–32], including 52148 patients. A total of seven retrospective cohort studies, three cross-sectional studies, one combined prospective and retrospective cohort study, and one Case series were involved. Table 1 lists the characteristics of the included studies.

Bias risk assessment of involved literature

The Newcastle–Ottawa Quality Assessment measured studies' quality. The quality scores of the studies ranged from seven to eight stars (Sup. Table 3).

Outcome indicators

Mortality

Evidence network A total of 12 studies reported mortality rates for five treatment regimens involving novel hypoglycemic agents in people with diabetes and COVID-19. The dot size indicates the size of the sample using the intervention and the thickness of the line shows the number of trials (Fig. 2A). The closed-loop inconsistency factor (IF) approached 1, as indicated by the result of the consistency test, and the lower limit of 95% CI covered 0, suggesting no significant inconsistency. Sup. Fig. 1 presents the results of the consistency test.

Publication bias As depicted in the funnel plot, most of the scatter points laid on either side of the vertical line, and they were essentially symmetric, probably exhibiting some publication biases (Fig. 3A).

Network meta-analysis Mortality was reported in 12 studies involving five treatment regimens, and network comparisons among the above-mentioned regimens yielded ten pairwise comparisons, of which two were statistically significant. The OR and 95% CI for SGLT2 compared with SGLT2i + GLP-1RA and DPP4i reached 0.41 (0.17,0.97) and 0.69 (0.49,0.98), respectively, as shown in Fig. 4A. The forest plots shown in Sup. Fig. 2.

SUCRA probability ranking The ranking of the five treatment options involving novel hypoglycemic agents, based on the area under the SUCRA curve, was as follows: SGLT2i > GLP-1RA > DPP4i > non-DPP4i > SGLT2i + GLP-1RA (Fig. 5A).

ICU

Evidence network Three studies report the endpoint of four treatment regimens involving novel hypoglycemic agents in people with diabetes and COVID-19 requiring intensive care unit (ICU) admission. The dot size indicates the size of the sample using the intervention, and the thickness of the line represents the number of trials, forming a closed loop (Fig. 2B).

Network meta-analysis Three studies reported requiring ICU admission involving four treatment options, and network comparisons among the above-described treatment options yielded a total of six pairwise comparisons, none of which were statistically significant (Fig. 4B). The forest plots shown in Sup. Figure 2.

SUCRA probability ranking Based on the area under the SUCRA curve, the four treatment options involving novel hypoglycemic agents were ranked as follows: SGLT2i > DPP4i > non-DPP4i > GLP-1RA (Fig. 5B).

Table 1 Characteristics of the included studies

Study	Study type	Sample	Age (years)	Male (%)	Metformin (%)	Statin (%)	Mortality (%)
Silverii (2021)[21]	Cross-sectional study	159	73.31 ± 12.66	NA	NA	NA	35.06%
Noh (2021)[22]	Retrospective cohort study	586	NA	NA	NA	NA	11.98%
Kahkoska (2021)[23]	Retrospective cohort study	12446	58.6 ± 13.1	46.60%	61.60%	27.20%	3.40%
Ramos-Rincón (2021)[24]	Cross-sectional study	2763	86 (82.7–88.9)	47.09%	53.50%	49.20%	48.70%
Orioli (2021)[25]	Retrospective cohort study	73	69 ± 14	52.00%	66.20%	35.60%	15.00%
Israelsen (2021)[26]	Prospective cohort study	616	59 (51–70)	53.00%	58.90%	50.00%	3.41%
Sourij (2020)[27]	Prospective and Retrospective cohort study	238	71.1 ± 12.9	63.60%	32.30%	NA	24.40%
Nyland (2021)[28]	Retrospective cohort study	29516	60.9 ± 15.0	48.20%	NA	NA	6.50%
Elibol (2021)[29]	Cross-sectional study	432	63.3 ± 10.3	45.60%	NA	NA	21.00%
Pérez-Belmonte (2020)[30]	Retrospective cohort study	2666	74.9 ± 8.4	61.90%	60.80%	58.00%	36.85%
Zhou (2020)[31]	Retrospective cohort study	2563	63 (55–67)	46.68%	NA	NA	2.93%
Mirani (2020)[32]	Case series	90	71 (64–78)	72.20%	76.67%	NA	42.22%

NA means Not Applicable

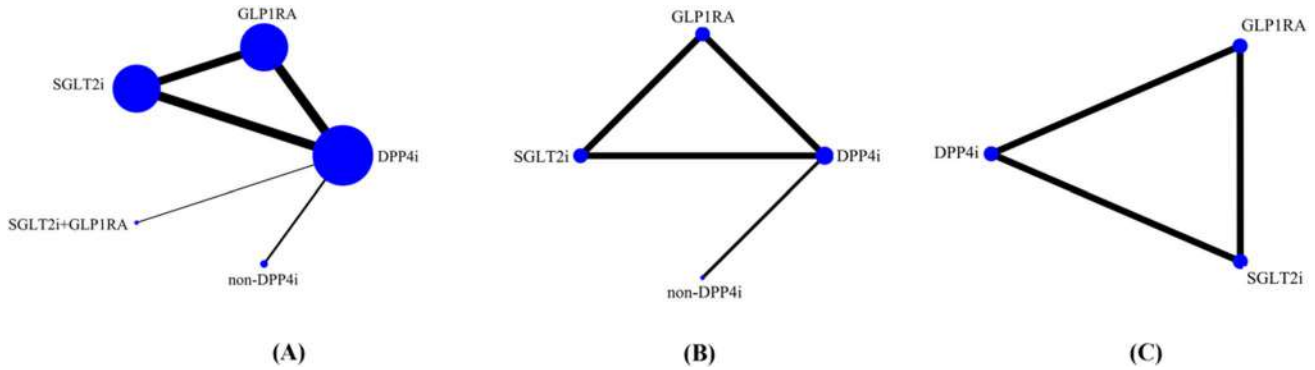

Fig. 2 Network diagrams of outcome indicators: (**A**) Mortality (**B**) ICU (**C**) Mechanical ventilation

Mechanical ventilation

Evidence network Two studies report the endpoint of three treatment regimens involving novel hypoglycemic agents in people with diabetes and COVID-19 requiring mechanical ventilation. The dot size indicates the size of the sample using the intervention, and the thickness of the line represents the number of trials, forming a closed loop (Fig. 2C).

Publication bias The funnel plot indicates that most scatter points are located in the middle or on one side of the vertical line (Fig. 3B). They are not symmetrical, suggesting the presence of publication bias.

Network meta-analysis Requiring mechanical ventilation was reported in 2 studies involving three treatment regimens, and network comparisons among the above-mentioned regimens yielded a total of 3 pairwise comparisons, of which one was statistically significant. The OR and 95% CI for SGLT2i compared with the DPP4i group reached 0.85 (0.75,0.97) (Fig. 4C). The forest plots are presented in Sup. Fig. 2.

SUCRA probability Ranking The ranking of the three therapeutic regimens involving novel hypoglycemic agents following the area under the SUCRA curve follows a descending order as follows: SGLT2i > GLP-1RA > DPP4i (Fig. 5C).

Discussion

In this study, the correlation between three novel glucose-lowering drugs and outcome indicators (mortality, requiring ICU admission, and requiring mechanical ventilation) in people with diabetes and COVID-19 was assessed. A total of 12 studies and three antidiabetic drugs (i.e., DPP4i, SGLT2i, and GLP-1RA) were covered in the analysis. As indicated by the results, in people with diabetes and COVID-19, mortality was significantly lower in the SGLT2i treatment group compared with the DPP4i group and the SGLT2i + GLP-1RA group. Requiring mechanical ventilation was significantly reduced in the SGLT2i group compared with the DPP4i

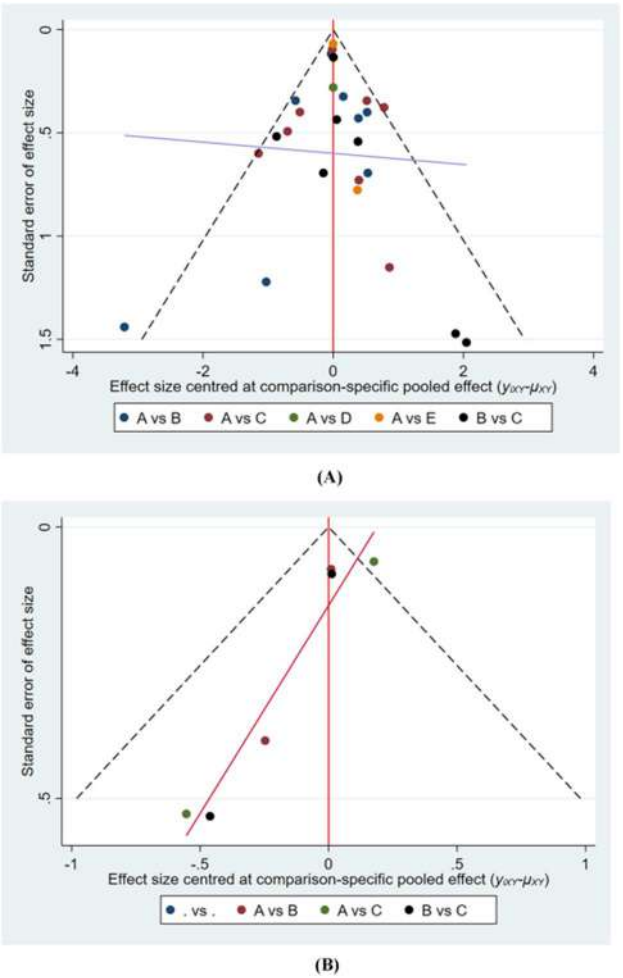

Fig. 3 Funnel plot outcome indicators: (**A**) Mortality (**B**) ICU. A: DPP4i, B:GLP1RA, C: SGLT2i

SGLT2i	1.11 (0.74,1.65)	**1.44 (1.02,2.04)**	1.92 (0.99,3.75)	**2.46 (1.03,5.88)**
0.90 (0.60,1.34)	GLP1RA	1.30 (0.92,1.84)	1.73 (0.89,3.37)	2.22 (0.93,5.30)
0.69 (0.49,0.98)	0.77 (0.54,1.09)	DPP4i	1.34 (0.76,2.35)	1.71 (0.77,3.80)
0.52 (0.27,1.01)	0.58 (0.30,1.12)	0.75 (0.43,1.32)	non-DPP4i	1.28 (0.48,3.40)
0.41 (0.17,0.97)	0.45 (0.19,1.07)	0.58 (0.26,1.30)	0.78 (0.29,2.07)	SGLT2i+GLP1RA

(A)

SGLT2i	1.09 (0.35,3.36)	1.29 (0.20,8.26)	1.67 (0.53,5.26)
0.92 (0.30,2.82)	DPP4i	1.18 (0.27,5.17)	1.53 (0.49,4.77)
0.78 (0.12,4.99)	0.85 (0.19,3.73)	non-DPP4i	1.30 (0.20,8.40)
0.60 (0.19,1.88)	0.65 (0.21,2.04)	0.77 (0.12,4.98)	GLP1RA

(B)

SGLT2i	1.08 (0.91,1.27)	**1.17 (1.04,1.33)**
0.93 (0.79,1.10)	GLP1RA	1.09 (0.94,1.26)
0.85 (0.75,0.97)	0.92 (0.79,1.07)	DPP4i

(C)

Fig. 4 Results from the NMA showing the effect of each of the interventions: (**A**) Mortality (**B**) ICU (**C**) Mechanical ventilation. The values in bold font represent statistically significant differences

group among diabetes and COVID-19 patients. As revealed by the above result, SGLT2i, among the three new hypoglycemic agents, is correlated with lower mortality and required mechanical ventilation in diabetes and COVID-19 patients.

SGLT2i is a unique class of glucose-lowering drugs primarily employed for the treatment of T2DM. The above class of drugs works by impairing the ability of the kidneys to absorb and filter glucose [33]. This drug exerts significant cardiorenal protective effects, especially in people subjected to atherosclerosis, heart failure, and decreased renal function [2, 34]. Moreover, existing research has suggested that this class of drugs can inhibit inflammation and fibrosis [34, 35]. An existing RCT study reported a lower but nonsignificant mortality rate in patients with diabetes administrated with dapagliflozin [36]. In COVID-19, SGLT2i reverses acid–base cytokine homeostasis by reducing lactate accumulation under the occurrence of hypoxemia and hypoxia, such that the decrease in cytoplasmic pH can be inhibited, and cellular damage can be prevented during cytokine storms [37]. The multiple effects of SGLT2i may be of potential benefit to COVID-19 patients, and SGLT2i may play a role in the future management of COVID-19[34, 38]. A previous meta-analysis has indicated that mortality is significantly lower in SGLT2i users compared with COVID-19 patients without SGLT2i [39, 40]. This study drew a conclusion that among with people with diabetes and COVID-19, mortality was significantly lower in the SGLT2i group compared with the DPP4i group and the SGLT2i + GLP-1RA group. Notably, there may be some controversy about the fact that the mortality rate of the SGLT2i group is lower than that of SGLT2i + GLP-1RA, the main possible reason for the result is that patients on both SGLT2i and GLP-1RA may have more severe diabetes and are associated with more mortality. Further relevant in vivo or in vitro model validation should be performed. Moreover, it is recommended that more standardized randomized controlled double-blind trials are needed in the future to provide a stronger basis for the safety and efficacy of novel glucose-lowering drugs for COVID-19 patients with diabetes. Requiring mechanical ventilation was significantly reduced in the SGLT2i group compared with the DPP4i group.

GLP-1 is generated by L cells in the distal ileum and proximal colon, binding to receptors in the pancreas, kidney, lung, gastrointestinal tract, as well as peripheral nervous system. Moreover, it is capable of stimulating insulin production, inhibiting glucagon release while delaying gastric emptying. GLP-1RA is another hypoglycemic agent that significantly reduces hospitalization, respiratory complications, and mortality in patients with diabetes [28]. In general, GLP-1RA acts on GLP-1 receptors in the lung epithelium and immune cells. GLP-1RA is capable of lowering blood glucose while controlling inflammation-induced lung damage and reducing major cardiovascular complications [2, 41]. Existing research [42] reported that GLP-1RA is capable of improving pulmonary function in patients with diabetes. In COVID-19, GLP-1RA is conducive to reducing cytokine-induced lung injury by interfering with the NF-kB pathway, or exerting anti-inflammatory effects [43, 44]. Two meta-analyses have confirmed the benefit of GLP-1RA in managing COVID-19, mainly in terms of lower mortality in GLP-1RA users compared with non-users [34, 38]. However, no correlation between GLP-1RA and mortality was identified in this study. The possible reason for this result is that the number of included studies in this study was limited and only compared among new hypoglycemic drugs.

An enzyme termed DPP-4 rapidly degrades GLP-1, i.e., DPP4i targets, a process that maintains the function of GLP-1 for more extended periods. DPP-4 is abundantly expressed

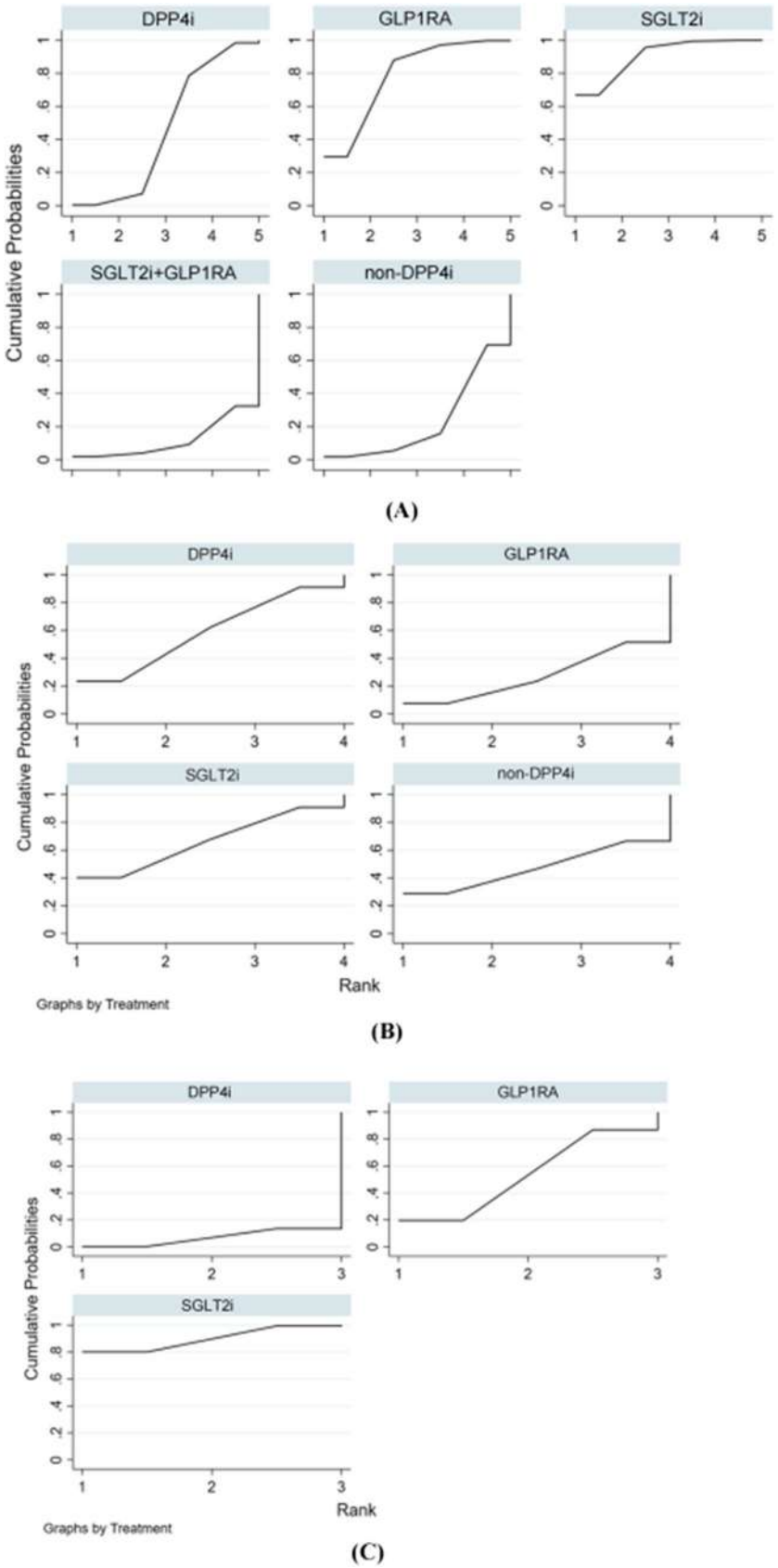

Fig. 5 Curve diagram of SUCRA of outcome indicators: (**A**) Mortality (**B**) ICU (**C**) Mechanical ventilation

in various cells (e.g., lymphocytes, adipocytes, endothelial cells, and lung epithelial cells), and is also present on the surface of different immune cells [45, 46]. DPP-4 takes on a critical significance to regulating inflammatory and immune responses through its ability to regulate various cytokines, chemokines, as well as peptide hormones [47, 48]. Given the role of DPP4i in regulating T-cell activity [45], the use of DPP4i has raised concerns regarding increased susceptibility to infection. However, no evidence in large clinical trials has demonstrated that using DPP4i can elevate the risk of infection [49, 50]. Uncertain anti-inflammatory properties are caused by the effect of DPP4i, which attenuates the activation of inflammatory vesicles and reduces the levels of inflammatory biomarkers (e.g., IL-6, IL-18, and CRP) in human plasma in some studies [51, 52]. Several studies have suggested that DPP4i exerts no effect on inflammatory biomarkers at the human plasma level [53, 54]. Nevertheless, DPP4i can potentially enhance the activity of certain inflammatory networks by preventing the degradation of inflammatory factors by the DPP4 enzyme [55]. Since DPP4i is capable of modulating inflammatory responses via multiple pathways, we hypothesized that they may have beneficial effects on patients prone to cytokine storming under the infection with COVID-19 [56]. Besides, no consistent conclusions have been reached regarding the correlation between DPP4i use and mortality in patients with combined diabetes mellitus and COVID-19. Some research has suggested that DPP4i use shows a correlation with lower mortality [39, 57, 58], and some previous studies have suggested that DPP4i can lead to increased mortality in people with diabetes and COVID-19 [40, 59]. Existing meta-analyses [11, 50, 60–63] indicated that DPP4i does not significantly affect COVID-19-associated mortality, which may also be related to the uncertain anti-inflammatory properties of DPP4i. This study found that DPP4 use was correlated with higher mortality and mechanical ventilation compared with SGLT2 in patients with combined diabetes mellitus COVID-19.

For the mortality, the ranking of the five treatment options involving novel hypoglycemic agents, based on the area under the SUCRA curve, was as follows: SGLT2i > GLP-1RA > DPP4i > non-DPP4i > SGLT2i + GLP-1RA. Notely, In our study, the SUCRA value of ICU was SGLT2i > DPP4i > non-DPP4i > GLP-1RA, but there was no significant difference among their ORs. The SUCRA value seems unreasonable. However, this phenomenon is not uncommon and has been addressed in several previous studies [64]. In particular, a potential bias in SUCRA does exist in the calculation, as SUCRA does not take into account the magnitude of effect differences between treatments, such interventions with wider CIs or fewer events may yield higher SUCRA values compared to some interventions with nonsignificant ORs. Respecting the mechanical ventilation, the ranking of the three therapeutic regimens involving novel hypoglycemic agents following the area under the SUCRA curve follows a descending order as follows: SGLT2i > GLP-1RA > DPP4i.

In summary, SGLT2i was more likely to be conducive to treating people with diabetes and COVID-19 among the above interventions included. The top interventions could be selected for patients with different goals.

Limitations

This study has some limitations. Firstly, this study included only observational studies, such that conclusions should be drawn with caution. However, we recruited the largest number of participants from a variety of studies of fair quality, allowing our meta-analysis to have high internal validity. Secondly, additional primary data mining is required because of the complexity of current diabetes treatment protocols. Thirdly is that due to the high publication rate on the COVID-19 topic within the past three years, some studies might be missed that were not included in this study. Although this was inevitable, we minimized this problem by assigning two investigators to systematically search and select studies and consulting with another investigator when necessary to reach a final decision.

Conclusion

In brief, this study aimed to assess the correlation between three novel glucose-lowering drugs and outcome indicators (mortality, requiring ICU admission, and requiring mechanical ventilation) in people with diabetes and COVID-19. To be specific, SGLT-2i was more likely to be conducive to treating people with diabetes and COVID-19. The above-described results may have implications for the clinical management of diabetes with COVID-19 and may inform the development of clinical practice guidelines or future RCT trials.

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Author contributions YY and LZ contributed to conception and design of the study and organized the database. CL performed the statistical analysis. YY wrote the first draft of the manuscript. LZ wrote sections of the manuscript. TK reviewed and edited the manuscript. YW made a critical review, commentary, and revision of the manuscript. All authors have read and approved the final manuscript.

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Data Availability Data supporting the finding of this study are available within the article text and tables.

Declarations

Ethics approval and consent to participate Not applicable.

Conflict of interest The authors declare no conflict of interest.

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REVIEW ARTICLE

The effect of exercise training on serum Omentin-1 levels, glycemic control and body composition in adults population: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background Omentin-1 has been acknowledged as an anti-inflammatory and insulin-sensitizing marker, which is mainly expressed in adipose tissue. Exercise training is a therapeutic intervention that can possibly improve and modify circulating Omentin-1 levels.

Objective To determine the effects of exercise training on circulating Omentin-1, glycemic control, and body composition in adult population.

Data sources Four electronic databases and reference lists of included articles were searched until February 5, 2023. The effect size of outcomes was summarized by calculating the mean difference (MD) with 95% confidence interval (CI).

Results Ten RCTs comprising 385 participants were included. The overall model revealed that exercise training increased Omentin-1 compared to the control (MD = 3.57 ng.ml; 95% CI, 1.80 to 5.34 ng.ml; $p < 0.001$). Subgroup analysis by exercise modalities revealed significant increases in Omentin-1 after isolated aerobic ($p = 0.002$) and resistance ($p < 0.001$) training but not after combined training. Subgroup analysis by sex indicated a significant improvement of Omentin-1 in women ($p = 0.015$) and men ($p = 0.007$). Furthermore, a significant increase was found in both healthy ($p = 0.035$) and non-healthy ($p = 0.002$) participants. Analysis of other outcomes indicated that exercise training significantly reduced glucose, insulin, insulin resistance, body weight, body mass index, and body fat, as well as improved lipid profiles.

Conclusion These findings reveal that isolated aerobic and resistance exercises resulted in an increase in serum levels of Omentin-1 in adults. More high-quality studies are required to clarify the mechanisms underlying the influence of exercise training on Omentin-1 concentrations.

Keywords Adipokines · Anti-inflammatory · Exerkine · Insulin resistance · Adipose tissue

Introduction

Metabolic disorders, such as type 2 diabetes, hypertension, and dyslipidemia, are becoming increasingly prevalent in the adult population, posing a significant challenge to healthcare systems worldwide [1–3]. Recent research has revealed that adipose tissue functions as an active endocrine tissue, releasing various bioactive molecules, including adipokines, that play a crucial role in energy homeostasis, blood pressure regulation, and glucose and lipid metabolism [4, 5]. Studies have reported a strong correlation between adipokines and the prevalence of metabolic disorders, suggesting that adipokines could potentially serve as therapeutic targets for the treatment of these conditions [6, 7]. Therefore, it is

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important to investigate the role of adipokines in the pathogenesis and treatment of metabolic disorders [8, 9].

Omentin-1 is a recently identified adipokine that has various isoforms, with Omentin-1 being the main form present in the bloodstream of humans [10]. Omentin-1 plays a crucial role in regulating insulin sensitivity, lipid metabolism, and lipolysis, and has been attributed with important functions such as anti-inflammatory and anti-atherosclerotic effects [11, 12], as well as regulation of high density lipoprotein production through stimulation of insulin receptor substrate [13, 14]. There is a growing body of evidence suggesting a strong association between Omentin-1 and dysmetabolic conditions such as insulin resistance, type 2 diabetes, and metabolic syndrome, as well as inflammatory response [15]. In this regard, a meta-analysis has revealed that omentin levels are significantly lower in individuals diagnosed with type 2 diabetes mellitus compared to controls, and reduced omentin levels are associated with an increased risk of complications in patients with diabetes [14, 16]. Omentin-1 has also been implicated in the development of obesity and obesity-related chronic disorders [17, 18]. Additionally, Omentin-1 has been demonstrated to improve energy balance, glucose metabolism, cardiovascular system function, and reduce oxidative stress [19, 20]. Hence, regulating Omentin-1 secretion and signaling may be important for both the management and mitigation of these adverse conditions [21].

Overall, Omentin-1 is a secretory factor that may act as both an endocrine factor, influencing systemic metabolism, including insulin action in subcutaneous adipocytes, and an autocrine/paracrine factor, regulating the biology of visceral adipose tissue locally [22, 23]. As such, investigating Omentin-1 has significant potential for identifying novel biomarkers and therapeutic targets for metabolic disorders.

Physical exercise is a critical non-pharmacological intervention for improving insulin sensitivity through a variety of metabolic and physiological alterations [24–26]. A growing body of evidence suggests that exercise training interventions may modify circulating Omentin-1 levels, which could have important implications for metabolic health. However, the literature on the effect of exercise on Omentin-1 levels has yielded inconsistent findings. Some studies have reported reductions in Omentin-1 levels after exercise training interventions [27], while others have observed increases [28–31]. Nevertheless, other investigations, such as that by Faramarzi et al. (2016), have reported no alterations in Omentin-1 levels following exercise training [32]. These discrepancies may be attributed to a wide range of factors, including differences in exercise modalities, duration, intensity, and frequency, as well as cohort features such as age, gender, and body composition.

Despite the growing interest in the potential effects of exercise training on circulating Omentin-1 levels, the general impact of exercise on serum Omentin-1 concentrations remains unclear due to inconsistent findings in the literature. To address this gap in knowledge, we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) in humans to investigate the impact of exercise training on Omentin-1 concentrations in adults. Our study aims to provide a comprehensive synthesis of the existing literature on this topic and to specifically investigate the effects of exercise training on Omentin-1 in adults, thus contributing to the broader understanding of the potential clinical implications of Omentin-1 as a biomarker and therapeutic target for metabolic disorders. In addition to our primary objective, we also assessed the effects of exercise training on insulin resistance, lipid profiles, and body composition in this population, providing valuable insights into the potential clinical benefits of exercise interventions for improving metabolic health.

Methods

We performed the current meta-analysis and systematic review based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [33]. This review was not registered.

Literature search

Four electronic databases, including PubMed, Medline, Web of Science, and Google Scholar were used for a detailed search by two investigators (AA and AN). The search utilized the following terms: ((((adult) AND (physical activity OR exercise)) AND Omentin/Omentin-1 AND human) NOT (child OR children OR adolescent OR rat OR mouse OR animal))). For additional eligible studies, reference lists of all relevant research, accompanied by reviews and book chapters, were also hand-searched. The search strategy covered the period from database inception until February 5, 2023. Two independent investigators read the titles and abstracts of the studies and filtered the related studies to include them in the text.

Article selection

To determine the study inclusion criteria, we considered the participants, intervention, comparison, outcome, and study design (PICOS) criteria. To qualify the studies in this review, three investigators (AA, RFM, and GhRMR) independently assessed the titles, abstracts, and full texts of the relevant articles to determine study eligibility. Qualified studies were required to meet the following criteria: (a) population: men and women (aged ≥ 18 years); (b) intervention: aerobic, resistance, or combined aerobic + resistance training, in which subjects did not take part in an exercise

training regimen within the prior 6 months; (c) comparison: non-exercise control group; (d) outcomes: Omentin-1, insulin resistance index, lipids, and body composition were used as outcome measures and measured at baseline and end of the intervention; (e) study design: RCTs published in the English language which comprised a comparison with non-exercise control groups.

Outcome measures

The primary outcome measure in the current study was serum Omentin-1 level at baseline and end of the intervention. The secondary outcome measures were glycemic factors (i.e., glucose, insulin, and HOMA-IR), lipid profiles, and body composition.

Data extraction

The data was extracted by two independent investigators (AA and RFM), and the discrepancies were resolved by the third reviewer (GhRMR). The information extracted included the following: details of publications (author, publication year, and country), characteristics of the study (the sample size for each group, health status, and exercise training modalities), characteristics of participants (mean or range age, gender), details of intervention (intervention period, frequency, intensity, duration, sets, and repetition), mean and standard deviation (SD) of the dependent variables at baseline, end of intervention, and/or changes between baseline and end of intervention. All values for Omentin-1 were recorded as ng.ml or converted to such if necessary.

Data synthesis

The effect size of each outcome was summarized by calculating the mean difference (MD) between the intervention and control groups from baseline and end of intervention for all included studies. Due to the similar methods of reporting techniques for outcomes, we utilized the MD with a 95% confidence interval (CI). The Comprehensive Meta-Analysis (CMA) software version 3.3.070 [34] was applied to conduct the analyses. Extracted outcome data was accomplished utilizing the change in the mean and SD values. The baseline mean was subtracted from the end of intervention mean, and the change SD was computed by applying study group subject numbers along with group p-values or 95% CI, where the change in mean and SD was not available. Where data were not revealed in text or tables and corresponding authors could not be contacted, data shown in figures was extracted or obtained where feasible by the GetData Graph Digitizer software. Where an article included a non-exercise control group and more than one exercise intervention group, we independently labeled each exercise intervention group and adjusted the sample size of the control group based on the number of exercise intervention groups. Because of the significant heterogeneity expected among studies, random-effects models were preferred.

The I^2 statistic [35] and Cochran's Q statistic [36] were used to establish heterogeneity. The I^2 ranges from 0 to 100%, where a value of 0% reflects no observed heterogeneity, and values of 25%, 50%, and 75% show low, moderate, and high heterogeneity, respectively [35]. Subgroup analyses comprising the effect of exercise training modalities, participants' gender, and health status of participants were considered to discover heterogeneity within main effects analyses. Meta-analysis was completed using Forest plots, and a 5% level of significance was considered to represent the significance of results.

Study quality

The Physiotherapy Evidence Database (PEDro) scale, which is an 11-item questionnaire considered to collect data on eligibility criteria, random allocation, concealed allocation, similarity of baseline values, blinding of participants, blinding of therapists and/or assessors, key outcomes, intention-to-treat analysis, between-group differences, point and variability measures, was applied to evaluate the methodological quality of the included studies [37]. This scale has been stated to be valid [38] and reliable [37]. Only those RCTs scoring ≥ 5 on the PEDro scale–a value considered to be of moderate to high quality [39] were considered for analysis. Two investigators (ANH and ShS) individually performed all quality assessments and any discrepancy was resolved by the third investigator (GhRMR).

Publication bias

To qualitatively assess publication bias, we used funnel plots of the effect size generated by Comprehensive Meta-Analysis software (version 2; Biostat Inc., Englewood, New Jersey, USA). Begg and Egger tests were used to assess funnel plot asymmetry, and a substantial publication bias was recognized if the P value was less than 0.10 [34]. To evaluate the effect of publication biases on the interpretation of the results, the trim and fill computation was assessed [34].

Results

Literature search

Initially, 580 papers were identified through database searches, with an additional five papers recognized via reference list searching. After title and abstract screening, 440 papers were omitted, leading to a full text review of

29 eligible studies. Nineteen other articles were removed for the reasons presented in Fig. 1. Ten articles met all inclusion criteria. The PRISMA flow diagram outlining this process is depicted in Fig. 1.

Cohort characteristics

Table 1 reveals the details of included studies. Briefly, when combined, 385 individuals (177 males; 208 females) participated in the studies. Four studies exclusively recruited male participants [28–30, 40]; five studies exclusively recruited female participants [27, 32, 41–43]; and one study recruited both males and females [44]. In 10 studies, the mean age of subjects ranged from 24.5 to 60.3 years. According to Health status classification criteria, four studies had participants who were classified on average as obese [28, 30, 32, 40], two as postmenopausal [42, 43], two as healthy [27, 29], one as type 2 diabetes [41] and one with coronary heart disease participants [44]. All the included studies were RCTs published between 2010 and 2022.

Description of included studies

Our 10 included RCTs (16 intervention groups) had an aggregate of 385 participants, 223 intervention participants, and 162 controls.

The intervention period of the investigations ranged from eight to 16 weeks, with each session's length ranging from 15 to 80 min. Of the 10 included studies, five [29, 30, 32, 43, 44] used only an aerobic exercise program, one examined high-intensity interval training program [28], one [42] explored circuit resistance training, one [27] comprised resistance, endurance and combined resistance + endurance, one [41] explored all three modalities (aerobic, resistance and combined aerobic + resistance), and one [40] comprised nonlinear resistance and aerobic interval training.

The most common types of aerobic exercise included walking, jogging, and running. The intensity of workouts ranged from 55–65% of maximal heart rate, and 65–70% of the symptomatic limit heart rate. Nevertheless, one study [43] did not report the intensity of exercise. The duration of the study of one RCT that used a high-intensity interval training regimen [28] was 12 weeks, include cycling at an

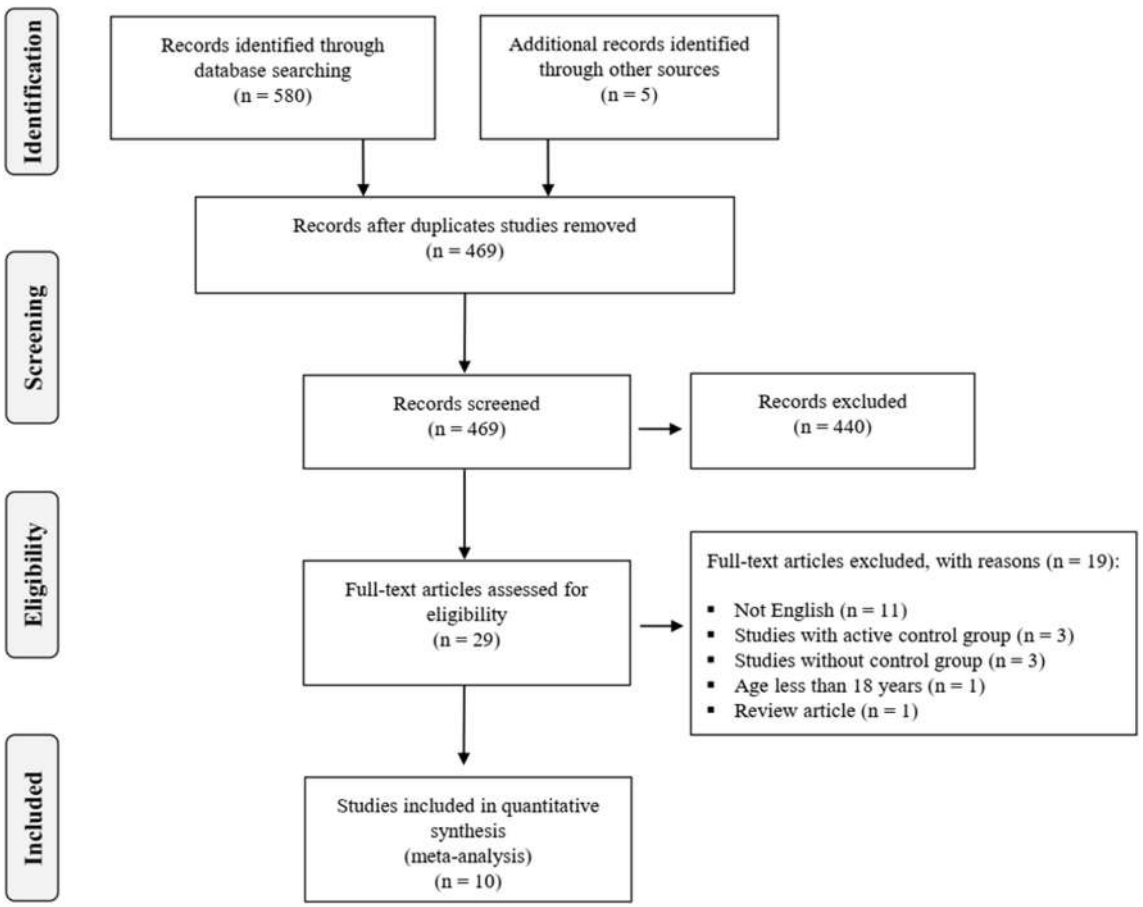

Fig. 1 Flowchart showing the process for the inclusion of studies

Table 1 Meta-analysis of exercise training included studies

Study; country	n INT (CON)	Age (yrs) Mean (SD)	Gender	Health status	Modes of exercise	INT group: frequency and duration	Omentin-1 measurement
AminiLari 2017; Iran	37 (15)	Ranged 45 to 60	Female	T2D	AT, RT, or CT	**AT group:** The warm-up phase comprised of 20 min of stretching and jogging. The main phase of the study was consisted of 25 min exercise in order to achieve 50% to 55% of maximum heart rate as measured by cycle ergometer. Running, exercise and stretching made up the cooling-down phase **RT group**: The warm-up involved 20 min of stretching exercises and jogging on the spot. The main phase consisted of three sets × eight repetitions of weight training including leg extension, prone leg curl, abdominal crunch, biceps, triceps, and seated calf. The exercise intensity was 50% to 55% of one-repetition maximum (1RM). The cooling-down also consisted of running, free exercises and stretching **CT group**: The main phase consisted of aerobic training integrated with RT, with half the execution time and the same intensity of resistance and aerobic groups. The trainings programs were performed within three sessions per week for 12 weeks. Every 2 weeks, in all exercise groups training was increased by 5 min and the intensity by 5%. The average intensity of main stage in every exercise group was 5.5 metabolic equivalent of task (MET) in first week and increased to 7.1 MET at the end of the study The training programs were performed within three sessions per week for 12 weeks	ELISA
Atashak 2022; Iran	15 (15)	INT: 24.5 (3.2) CON: 25.3 (3)	Male	Obesity	HIIT	Each of the prescribed sessions began with a 5 min warm-up cycling at a moderate intensity corresponding to 40–50% of each participant's HRmax cycling exercise (each lasting 2 min) at an intensity of 85–95% HRmax, followed by 1 min of passive recovery between each bout HIIT started with 85% of HRmax during the first four weeks with 1 min passive recovery periods between each exercise. bout and increased by 5% in each subsequent 4-week period so that the intensity of training reached 95% HRmax with 1 min passive recovery between each exercise bout at the end of the 12th week At the end of each training session, there was a 5-min cool-down period involving slow cycling and gentle stretching	ELISA
Banitalebi 2016; Iran	31 (9)	Total 60.3	Female	Healthy	E + S S + E CI	The exercise intervention was eight weeks of combined (resistance plus endurance) training. Experimental groups underwent training three times per week. Each session consisted of 10 min of general warm up, 50 min of exercise training, and 10 min for cooling-down processes	ELISA

Table 1 (continued)

Study; country	n INT (CON)	Age (yrs) Mean (SD)	Gender	Health status	Modes of exercise	INT group: frequency and duration	Omentin-1 measurement
Faramarzi 2015; Iran	19 (16)	Ranged 25 to 45	Female	Obesity	AT and Core stability	The exercise intervention was 12 weeks of rhythmic aerobic exercise plus core stability training. 3 times per week-each session 10 min general warm-up 30 min rhythmic aerobic exercise and 30 min core stability training and 10 min for cooling processes	ELISA
Mousavi 2022; Iran	21 (18)	INT: Nonsmoker 28 (2.7) Smoker 30.5 (1.7) CON: Nonsmoker 27.6 (2.5) Smoker 29.3 (2.5)	Male	Healthy	AT	The aerobic training program was performed 20–35 min a day, 3 days a week for eight consecutive weeks. Each session was executed in three continuous stages as follows: warm-up by exercises including marching, walking briskly, and jogging for 10 min; main activity (aerobic training program); and cooldown by walking, slow jogging and typical post-running stretches for 10 min The exercise sessions lasted 20 min and the initial intensity of training was set at 55–65% of an individual's maximal heart rate (HRmax) for the first four weeks and was progressively increased to 70% of HRmax for 35 min in the 8th week of the protocol	ELISA
Nikseresht 2016; Iran	22 (11)	NRT grp 40.4 (5.2) AIT grp 39.6 (3.7) CON 38.9 (4.1)	Male	Obesity	NRT, AIT	NRT: The NRT program involved different intensities with flexible periodization and consisted of 55 min of weight training per session and 3 sessions per week for 12 week AIT: AIT included running on a treadmill (4 × 4-min intervals at 80%–90% of maximal heart rate, with each interval separated by 3 min at 65%). The intensity of the training program was controlled by using a heart rate monitor	ELISA
Saeidi 2019; Iran	12 (12)	INT: 58 (5) CON: 56 (5)	Female	Postmenopausal	CRT	Participants in the EG group performed movements at 55% of 1-RM for 8 weeks (3 sessions per week) Each exercise session included a 5 min warm-up and then followed by the 12 prescribed exercises, with duration of approximately 30 s at each exercise station. The number of repetitions at each station was recorded for the participants. In each session, two sets (turns) of 12 exercises were carried out such that between each set, there was a 3 min active rest period	ELISA
Saremi 2010; Iran	9 (9)	43.1 (4.7)	Male	Obesity	AT	It was performed 50–60 min a day, 5 days a week for 12 weeks. The training program began at 60–65% of maximal heart rate and gradually increased to 80–85% of maximal heart rate by week 12. Aerobic training included treadmill walking/running	ELISA

Table 1 (continued)

Study; country	n INT (CON)	Age (yrs) Mean (SD)	Gender	Health status	Modes of exercise	INT group: frequency and duration	Omentin-1 measurement
Wang 2019; China	50 (50)	INT: ranged 42 to 59 CON: ranged 41 to 56	Both	Coronary heart disease	AT	walking and walking up and down stairs slowly, 5–10 min at a time, once in the morning, once in the middle and once in the evening; (2) they gradually increased the intensity of exercise after discharge, the form of exercise was plain walking, the target rate was controlled at 65%-70% of the symptomatic limit heart rate and the exercise was conducted once in the morning and once in the evening	ELISA
Yates 2018; USA	7 (7)	INT: 57.5 (4.4) CON: 55.8 (5.2)	Female	Postmenopausal	AT	The lifestyle intervention was based on the 16-week Diabetes Prevention Program and was delivered as 16 weekly in-person sessions. Participants were provided with individualized calorie goals based on activity level, age, height, and weight, along with a dietary fat intake goal of 25% calories from fat. Participants were instructed to record dietary intake daily, including calculation of total calories and grams of dietary fat consumed, and weigh themselves weekly. Additionally, participants were provided a pedometer to monitor their daily step counts, and worked with study personnel to set up daily step goals. They were also offered the opportunity to participate in two supervised exercise sessions per week	ELISA

Abbreviations: *n*, Number; *INT*, Intervention; *CON*, Control; *SD*, Standard deviation; *T2D*, Type 2 diabetes; *AT*, Aerobic training; *RT*, Resistance training; *CT*, Combined training; *1RM*, One repetition maximum; *BMI*, Body mass index; *HIIT*, High-intensity interval training; *HRmax*, Maximum heart rate; *TG*, Triglyceride; *TC*, Total cholesterol; *HDL*, High-density lipoprotein; *LDL*, Low-density lipoprotein; *E + S*, Endurance + strength; *NRT*, Nonlinear resistance training; *AIT*, Aerobic interval training; *CRT*, Circuit resistance training; *ELISA*, Enzyme-linked immunosorbent assay

intensity of 85–95% maximum heart rate, followed by one minute of passive recovery between each bout.

Effect of exercise on Omentin-1

Ten studies (16 arms) were analyzed for Omentin-1 as revealed in Fig. 2. Overall, exercise interventions resulted in an increase in the Omentin-1 level (MD = 3.57 ng.ml; 95% CI [1.80 to 5.34 ng.ml]; $p < 0.001$; $I^2 = 84\%$; p for heterogeneity < 0.00001). Subgroup analyses are revealed in Supplemental Table 1. There was a significant increase in the Omentin-1 level for the 9 arms reporting the level of Omentin-1 for aerobic exercise interventions (MD = 3.54 ng.ml; 95% CI [1.25 to 5.83 ng.ml]; $p = 0.002$). Moreover, the 3 arms aimed at resistance training evidenced a significant increase in the Omentin-1 level of 2.83 ng.ml (95% CI [1.36 to 4.30 ng.ml]; $p < 0.001$). However, the 4 arms applying a combined aerobic and resistance training protocol discovered a non-significant change in Omentin-1 levels of 4.61 ng.ml (95% CI [-2.39 to 11.62 ng.ml]; $p = 0.197$). Subgroup analysis by sex indicates a significant improvement of Omentin-1 in women (MD = 3.56 ng.ml, $p = 0.015$) and men (MD = 5.43 ng.ml, $p = 0.007$). Furthermore, a statistically significant increase was found in both studies with healthy participants (MD = 2.97 ng.ml, $p = 0.035$) and non-healthy participants (MD = 4.41 ng.ml, $p = 0.002$).

Effect of exercise on glucose, insulin, and HOMA-IR

Seven studies (11 arms) providing a total of 221 participants reported fasting glucose as an outcome measure. Pooled results demonstrated that exercise training significantly reduced glucose levels (MD = -5.92 mg/dl; 95% CI, -10.03 to -1.81 mg/dl; $p < 0.001$; $I^2 = 63\%$; p for heterogeneity = 0.002; Table 2). A comparison of glucose levels based on the mode of exercise training revealed that glucose levels decreased significantly when isolated aerobic (MD = -5.24, $p = 0.30$) and resistance training (MD = -14.03, $p = 0.018$) were used. Another subgroup analyses revealed that glucose levels reduced in studies with male participants (MD = -8.83, $p < 0.001$), as well as in studies with healthy participants (MD = -9.43, $p < 0.001$; Supplemental Table 1).

There was a significant pooled MD for the effectiveness of exercise training programs on insulin levels (-1.52; 95% CI, -2.56 to 0.49; $p = 0.004$, $I^2 = 40\%$; nine intervention arms; Table 2). A comparison of insulin levels based on sex revealed that insulin concentrations reduced significantly only in men (MD = -1.77 [-3.08 to -0.46], $p = 0.008$) but not in women (MD = -0.92 [-2.90 to -0.91], $p = 0.362$). Moreover, subgroup analyses based on health status revealed significant reductions only in healthy subjects (MD = -2.44 [-3.32 to -1.56], $p < 0.001$; Supplemental Table 1).

HOMA-IR was significantly reduced, with an MD of − 0.62 (95% CI, − 0.82 to − 0.42; $p < 0.001$) (Table 2). Both healthy and non-healthy participants revealed a significant reduction in HOMA-IR, with an MD of -0.72 (95% CI, -0.90 to -0.53; $p < 0.001$) and -0.45 (95% CI, -0.82 to -0.07; $p = 0.019$), respectively. Moreover, subgroup analyses based on sex revealed that HOMA-IR decreased significantly in both men (MD = -0.60 [-0.87 to -0.33], $p < 0.001$) and women participants (MD = -0.62 [-1.08 to -0.16], $p = 0.008$) (Supplemental Table 1).

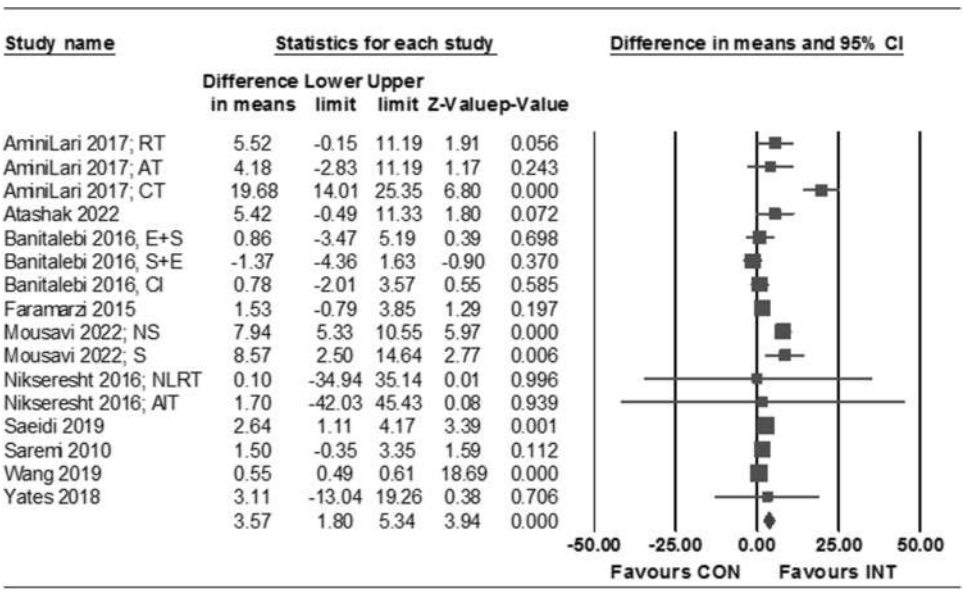

Fig. 2 Forest plot for the Omentin-1. RT, resistance training; AT, aerobic training; CT, combined training; E + S, endurance + strength; S + E, strength + endurance; CI, combined intervention; NS, non-smoker; s, smoker; NLRT, non-linear RT; AIT, aerobic interval training

Table 2 Full results of secondary outcomes

Variable	N. arms	MD (95% CI)	*p*-value	p-heterogeneity	I^2
Glucose (mg.dl)	11	-5.92 (-10.03, -1.81)	< 0.001	0.002	63%
Insulin	9	-1.52 (-2.56, -0.49)	0.004	0.100	40%
HOMA-IR	8	-0.62 (-0.82, 0.42)	< 0.001	0.306	15%
TG (mg.dl)	7	-16.48 (-21.91, -11.05)	< 0.001	0.521	0%
TC (mg.dl)	6	-12.63 (-18.23, -7.04)	< 0.001	0.901	0%
HDL (mg.dl)	7	3.11 (0.34, 5.88)	0.028	0.042	54%
LDL (mg.dl)	7	-7.64 (-14.49, -0.78)	0.029	0.031	56%
Body mass (kg)	14	-2.18 (-3.16, -1.19)	0.003	1.000	0%
BMI ($kg.m^2$)	12	-0.82 (−1.17, −0.47)	< 0.001	1.000	0%
Body fat (%)	12	-2.12 (-2.66, -1.57)	< 0.001	0.926	0%

MD, mean difference; *CI*, confidence interval; *TG*, triglyceride; *TC*, total cholesterol; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *BMI*, body mass index

Effect of exercise on lipids

Table 2 illustrates the results for lipids. Statistically significant reductions were found for triglyceride after exercise interventions (-16.48 mg/dl [-21.91 to -11.05], $p < 0.001$). Total cholesterol and low-density lipoprotein were also significantly reduced after exercise regimens (-12.63 mg/dl [-18.23 to -7.04], $p < 0.001$ and -7.64 mg/dl [-14.49 to -0.78], $p = 0.029$, respectively). Inversely, high-density lipoprotein was significantly increased after exercise training regimens (3.11 mg/dl [0.34 to 5.88], $p = 0.028$).

Effect of exercise on body composition

Body weight was significantly reduced, with an MD of − 2.18 kg (95% CI, − 3.16 to − 1.19 kg; $p < 0.001$) (Table 2). Non-healthy participants had a larger and significant reduction in body weight, with an MD of -2.38 kg (95% CI, -3.53 to -1.23 kg; $p < 0.001$) than healthy participants (MD = -1.62 kg; 95% CI, -3.53 to 0.30 kg; $p = 0.10$). Moreover, studies with male participants revealed a larger reduction in body weight, with an MD of -3.40 kg (95% CI, -5.66 to -1.14 kg; $p = 0.003$) than those with female participants (MD = -1.89 kg; 95% CI, -2.99 to -0.80 kg; $p = 0.001$) (Supplemental Table 1).

BMI was significantly reduced, with an MD of − 0.82 kg.m^2 (95% CI, − 1.17 to − 0.47 kg.m^2; $p < 0.001$) (Table 2). Non-healthy participants had a larger reduction in BMI, with an MD of -0.86 kg.m^2 (95% CI, -1.27 to -0.45 kg.m^2; $p < 0.001$) than healthy participants (MD = − 0.71 kg.m^2; 95% CI, − 1.38 to -0.05 kg.m^2; $p = 0.036$). Also, studies with male participants had a larger reduction in BMI, with an MD of -0.95 kg.m^2 (95% CI, -1.59 to -0.32 kg.m^2; $p = 0.003$) than those with female participants (MD = -0.76 kg.m^2; 95% CI, -1.18 to -0.34 kg.m^2; $p < 0.001$) (Supplemental Table 1).

Body fat was significantly reduced, with an MD of -2.12% (95% CI, -2.66 to -1.57%; $p < 0.001$). Non-healthy participants had a larger reduction in body fat, with an MD of -2.31% (95% CI, -3.18 to -1.45%; $p < 0.001$) than healthy participants (MD = -1.99%; 95% CI, -2.68 to -1.30%; $p < 0.001$). Furthermore, studies with male participants had a larger reduction in body fat, with an MD of -2.59% (95% CI, -3.62 to -1.55%; $p < 0.001$) than those with female participants (MD = -1.94%; 95% CI, -2.57 to -1.30%; $p < 0.001$) (Supplemental Table 1).

Quality assessment

Supplemental Table 2 shows the quality assessment of the included studies. Overall, the median PEDro score was 6/11 points (ranging from 5 to 8).

Publication bias

The funnel plot, including the Egger regression test for the Omentin-1 analyses, did not suggest publication bias, nor did Duval and Tweedie's trim and fill computation change the results. Moreover, funnel plots, including Egger regression tests for other analyses, did not suggest publication bias, nor did Duval and Tweedie's trim and fill computation change the results (see Supplemental Figs. 1–11).

Discussion

The primary purpose of the present study was to undertake a systematic review and meta-analysis of RCTs considering the effects of exercise training regimens on Omentin-1 levels in adults. The second purpose was to estimate the impact of exercise training protocols on insulin resistance, lipid profiles, and body composition in this population. The meta-analysis found a statistically significant increase in serum Omentin-1 levels among participants who underwent exercise training interventions. In addition, exercise training

resulted in significant improvements in HOMA-IR, glucose and insulin levels, lipids, and all body composition parameters, including body weight, BMI, and body fat. Meanwhile, subgroup analyses according to the type of exercise interventions (aerobic, resistance, and mixed of them), the health status (healthy and non-healthy), and sex (men, women, and both) revealed that exercise training had statistically similar results across these subgroups (Supplemental Table 1).

Recent evidence [6, 45, 46] has confirmed that an improvement in serum adipokine concentrations can lower the risk of various diseases such as obesity, diabetes, and cardiovascular disease, suggesting the potential role of adipokines as therapeutic targets in this regard. Among adipokines, Omentin-1 can disclose the pathophysiology of obesity and insulin resistance [47] by reflecting anti-inflammatory effects in obesity-related cardiometabolic disorders [48]. It has been revealed that Omentin-1 increases insulin action by activating protein kinase B to improve insulin signaling and glucose uptake by adipocytes [22, 49].

Exercise training interventions have been suggested to improve the circulating levels of several adipokines [50]. Previous research has shown, for example, that different exercise training modalities might have therapeutic targets in various populations by increasing plasma or serum adiponectin and decreasing leptin concentrations [46, 51, 52]. Nevertheless, the effects of exercise regimens on Omentin-1, an anti-inflammatory adipokine secreted by visceral adipose tissue [22, 30], still remain unclear in different populations. The findings of the current study revealed that exercise training increased serum Omentin-1 levels in adults.

In adipose tissue, Omentin-1 has been identified as one of the first molecules to exhibit a significant difference in gene expression between visceral and subcutaneous fat depots [22]. Additionally, Omentin-1 has been shown to enhance the effect of insulin action on glucose metabolism, suggesting a potential role in insulin sensitivity [49]. As a secretory factor, Omentin-1 may also act as both an endocrine factor to modulate systemic metabolism and an autocrine and paracrine factor to regulate adipose tissue biology locally [22]. Since Omentin-1 circulates in the blood, it may have effects on distant tissues such as muscle, liver, and subcutaneous fat to enhance insulin sensitivity and glucose metabolism, suggesting a wider role in nutrient storage and partitioning. As subcutaneous fat involves more than 80% of the adipose tissue in the human body, the fact that Omentin-1 circulates systemically and potentiates insulin action in subcutaneous fat may be of physiological and pathophysiological importance [22]. While the clinical applications of Omentin-1 are not yet fully established, our findings are consistent with the findings of Jung et al. (2021) and suggest that Omentin-1 may have significant potential as a newly identified hormone with important roles in adipose tissue and systemic metabolism. Furthermore, our study suggests that Omentin-1 could be a promising therapeutic target for metabolic disorders and a valuable biomarker for assessing metabolic health [53].

The exact mechanism for exercise-induced increases in the level of Omentin-1 has not been acknowledged yet. Nonetheless, some main possibilities could be suggested for the association between serum Omentin-1 concentrations and exercise training in our study. Firstly, Omentin-1 concentrations have been reported to correlate with improved plasma lipids due to weight loss [54] and/or physical exercise [31]. In this context, our results reveal that exercise training regimens were associated with significant improvements in lipid profiles. Omentin has been demonstrated to enhance the phosphorylation of 5-AMP-activated protein kinase, which inhibits the synthesis of endogenous cholesterol [55]; therefore, it seems that Omentin-1 has a remarkable role in regulating lipid metabolism and also acts against diabetic dyslipidemia as a compensatory mechanism [56]. Moreover, Omentin-1 was suggested to have an anti-atherogenic behavior; as a result, it can affect the level of high-density lipoprotein by modulating insulin action [19, 57]. Secondly, it has been stated that an improvement in body composition parameters is one other of the probable mechanisms to explain the Omentin-1 increase following exercise training [30, 56], which was observed in our study. In this regard, studies have established that weight management or loss through lifestyle interventions (exercise training along with dietary modification) meaningfully resulted in increased basal Omentin-1 concentrations in a range of populations, accompanied by additional improvements in body composition and metabolic profile [30, 31, 56]. Nevertheless, Wilms and colleagues (2015) observed an increase in Omentin-1 concentrations without a profound change in body weight [31]. On the other hand, the results of Faramarzi et al. (2015), one of the included studies in our meta-analysis, demonstrated significant decreases in BMI and body fat without profound alterations in plasma levels of Omentin-1, glucose, insulin, and HOMA-IR [32]. These controversial findings may reveal that Omentin-1 secretion is very sensitive to exercise and may rise even without the induction of a negative energy balance. In addition, other explanations for the inconsistency in these findings might derive from dissimilarities in the applied exercise training protocols (i.e., intensity, duration, and modality). Undoubtedly, these ideas need additional examination.

Another explanation is that weight loss improves insulin sensitivity, which leads to an increase in Omentin-1 as it has been evidenced that hyperinsulinemia is an inhibitor of Omentin production [58]. A number of studies have verified the function of Omentin-1 in facilitating insulin signaling through the activation of kinase B protein/Akt and enhancing glucose uptake stimulated by insulin into adipose tissue [59]. It has been shown that Omentin-1 has the potential to enhance glucose metabolism and insulin sensitivity through

the facilitation of glucose transport into the muscles subsequent to exercise training [13]. The study conducted by Castro et al. (2019) revealed a relationship between omentin-1 and skeletal muscle as well as adipocytes [13]. According to Alizadeh et al. (2017), exercise training results in an elevation in omentin gene expression in adipose tissue and thus enhances insulin sensitivity [60]. Moreover, Omentin secretion by adipocytes is related to the physiological adaptation of skeletal muscle to exercise training [31]. Therefore, independently of the insulin effect, exercise training alters circulating Omentin-1 levels and impacts skeletal muscle glucose metabolism via protein kinase B. Nevertheless, additional studies are required to examine Omentin-1 concentrations during chronic exercise training regimens.

The current review has some strengths. First, we adopted a three-step search strategy for four databases, reference lists, specialized journals, and gray literature. Second, we chose only the RCT design due to its credibility. Nevertheless, we believe that there are also some limitations in our study. First, only 10 RCTs with a total of 385 participants were studied. According to this, further trials with large sample sizes are needed to deliver more definitive findings, and the findings should be interpreted with caution. Second, in this review, statistical heterogeneity is evident. Despite the fact that subgroup analyses were undertaken to identify possible sources of heterogeneity, the high levels of heterogeneity cannot be adequately and rationally explained. Third, one of the most essential limitations of our meta-analysis is that we did not register our protocol with PROSPERO, which is the major registration platform for systematic reviews and meta-analyses. Finally, while all the included studies in our meta-analysis used enzyme-linked immunosorbent assay (ELISA) kits to measure serum Omentin-1 concentrations, not all the studies provided detailed information on the features of the ELISA kits used, such as assay range, assay sensitivity, or minimal detectable concentration for Omentin-1. This limitation means that it was not possible to provide a comprehensive comparison of different assay methods used for estimating Omentin-1 in different RCTs, which may affect the comparability of the results across the studies.

Conclusion

The overall conclusion of this meta-analysis was that exercise training interventions raised serum Omentin-1, reduced glucose, insulin, body weight, BMI, and body fat, as well as improved lipids and insulin resistance. Nevertheless, isolated aerobic and resistance exercise interventions significantly affected the serum levels of Omentin-1, but not combined aerobic plus resistance exercises. Further high-quality investigations are required to clarify the mechanisms underlying the influence of exercise training on Omentin-1 concentrations.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13410-023-01229-w.

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Data availability As this is a systematic review and meta-analysis, all relevant data are included in the paper.

Declarations

Ethics approval and consent to participate Not applicable.

Conflict of interest The authors report no declarations of interest.

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REVIEW ARTICLE

Surrogate markers of metabolic syndrome and insulin resistance in children and young adults with type 1 diabetes: a systematic review & meta-analysis (MetS and IR in T1DM)

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Abstract

Objective Metabolic syndrome (MetS) and insulin resistance (IR) are associated with diabetes. Insulin therapy in type 1 diabetes (T1DM) may complicate the diagnosis of both these conditions. Therefore, investigation of the diagnostic efficacy of MetS and IR components is important in paediatric population with type 1 diabetes mellitus (T1DM).

Methods SCOPUS, Web of Science, and PubMed were searched for studies that have MetS and IR in paediatric populations with T1DM. We assessed the strength of association for MetS and IR components. A random effect model was used for the meta-analysis and the effect size was reported in terms of Hedge's g.

Results A total 30 studies were identified relevant to our systematic search. Insulin dosage and HbA1c, markers for glycemic condition showed very small effect on MetS with T1DM. In the lipid profile, triglyceride (TG) and low-density lipoprotein (LDL) showed better effect size than high-density lipoprotein (HDL). In case of IR, heterogeneous nature of studies made it difficult to carry out a meta-analysis. A descriptive review of existing and novel markers is thus provided.

Conclusion In children with T1DM, lack of association between markers of glycemic condition suggested that MetS may develop independent of glycemic level. Other than TG and HDL, LDL may be used in the diagnosis of MetS. A universally accepted diagnosis protocol would enhance accuracy and comparability across research and clinical settings, as observed in the descriptive review.

Keywords Biomarkers · Insulin resistance · Metabolic syndrome · Type 1 diabetes · Children

Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune condition which results in the loss of pancreatic beta cells. This leads to dependency of the person on exogenous insulin therapy. The peak age for T1DM diagnosis is 5-9yrs and 10-14yrs with the prevalence increasing among young individuals [1, 1–5]. People with recently diagnosed T1DM generally have a lower body mass index; however, obesity rates has risen in this population [6]. Notably, metabolic syndrome (MetS) and insulin resistance (IR) can also be observed in lean individuals with T1DM [7–9]. MetS and IR are the risk factors for cardiovascular diseases (CVD). Therefore, diagnosis and management of MetS and IR are crucial for the prevention of cardio metabolic risks.

The prevalence of MetS in people with T1DM is suggested to be 23.7% and is increasing [10, 11]. The diagnosis of MetS is based on three different criteria that are laid down by the World health Organization (WHO), the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III), and the International Diabetes Federation (IDF) [12]. These criteria are based on anthropometric measurements such as waist circumference (WC), hypertension (HTN) and biochemical parameters such as the lipid profile (Table 1).

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Table 1 Diagnostic criteria for metabolic syndrome according to different organization

Criteria laid by	Components of MetS	Cut-offs for adults
WHO (1998) [13]	Insulin resistance (by impaired fasting glucose (FG) or impaired glucose tolerance (IGT) or Hyperinsulinemic Euglycaemic Clamp (HEC)) with (any 2 of the following: obesity, dyslipidemia, high systolic, high diastolic blood pressure, increased urine microalbumiuria)	FG > 100 mg/dl, IGT > 140 mg/dl 120 min after ingestion of 75 g of glucose, WHR: ≥ 0.90(M), 0.85(F) or BMI ≥ 30 kg/m2, TG ≥ 150 mg/dl or HDL-C ≤ 35 mg/dl(M), 39 mg/dl(F), BP ≥ 160/90 mmHg, Urinary albumin excretion of 20 µg/min or albumin-to-creatinine ratio of 30 mg/g
NCEP ATP III (2005 revised) [12]	Any 3 of five: Obesity, Hyperglycemia, dyslipidemia, high systolic or high diastolic BP	Waist circumference: ≥ 40 inches (M), ≥ 35 inches (F), Fasting glucose ≥ 100 mg/dl or Rx, TG ≥ 150 mg/dl or Rx, HDL cholesterol ≤ 40 mg/dl (M), ≤ 50 mg/dl (F); or Rx, HTN ≥ 130 mmHg systolic or ≥ 85 diastolic or Rx
IDF(2007) [14]	Central obesity (by waist circumference) with (2 of the four criteria: FG, TG, HDL, BP) *If BMI > 30 kg/m^2 central obesity can be assumed	Waist circumference: ≥ 94 cm(M), ≥ 80 cm(F), FG ≥ 100 mg/dl, TG ≥ 150 mg/dl, HDL ≤ 40 mg/dl(M), ≤ 50 mg/dl(F), BP ≥ 130 mmHg or ≥ 85 mmHg diastolic or Rx

WHR waist to hip ratio, *HDL* High Density Lipoprotein, *BP* Blood Pressure, *BMI* Body Mass Index, *Rx* on drugs of management for the condition

Most of the cut-offs for the diagnosis of MetS are developed for the adult population [15–17]. These parameters are modified only by changing the threshold for use in paediatric population. Along with MetS, the prevalence of IR in children with T1DM termed as double diabetes is also risen in children [18–22].The term double diabetes has been used to refer to individuals with T1DM who are overweight, have family history of diabetes, and have clinical features of insulin resistance [18]. Factors such as food habits, reduced physical activity, gender, age, and genetic predisposition may contribute to the development of IR in children with T1DM [23, 24]. Presence of IR in children with T1DM increases the risk of development of various macro and microvascular complications [25]. Hence, the diagnosis of IR may help clinicians to implement preventive measures or add an adjuvant therapy.

The diagnosis of IR in Type 2 diabetes (T2DM) depends on measurement of fasting insulin levels which are negligible in T1DM. Therefore, the indices used for the diagnosis of IR in T2DM have little use in T1DM. The gold standard method for the diagnosis of IR in children with T1DM is the Hyperinsulinemia Euglycemic Clamp (HEC) in which the glucose concentration is maintained by variable infusion of exogenous glucose and insulin [26]. However, the HEC technique is expensive, and space and time consuming. Therefore, various alternate methods have been developed for the diagnosis of IR that rely on indirect markers such as estimated glucose disposal rate (eGDR) [27–30], Insulin Sensitivity Score (ISS) [31] and, insulin sensitivity equation (eIS) [32] provided by Epidemiology of Diabetes Complications (EDC), Search for diabetes in youth (SEARCH), and Coronary Artery Calcification in T1DM (CACTI) respectively (Table 2).

The indices for IR in T1DM have been validated by direct comparison with HEC [8, 31, 35, 36]. There are no threshold or cut-offs provided for these indices. However, many authors have provided cohort based thresholds. Most of these studies include adults with T1DM (Supplementary Table 1) [37–41]. The exogenous insulin administration and pubertal age may interfere with the existing parameters of MetS and IR. Therefore, a systematic review and meta-analysis is needed for both these conditions.

Table 2 Indices provided for calculation of insulin resistance in Type 1 diabetes

Groups	Equations	Target population
IDF (2007) [33]	eGDR = 24.31–12.22 × (WHR)-3.29 × (HTN)-0.57 × (A1C[%])	Adult participants with T1DM (compared with HEC)
SEARCH (2011) [8, 31, 34]	IS scores = Exp(4.64725–0.02032(waist[cm])-0.09779(HbA1c[%])-0.00235(TG[mg/dlL]))	Adolescence participants with T1DM, T2DM and with no diabetes (compared with HEC)
CACTI (2011) [35]	eIS = Exp(4.1075–0.01299 × (waist[cm])-1.05819 × (insulin dose)-0.00354 × (TG[mg/dL)-0.00802 × (DBP[mmHg]))	Adult participant with T1DM (compared with HEC)

EDC Epidemiology of Diabetes Complications, *SEARCH* SEARCH for Diabetes in Youth, *CACTI* Coronary Artery Calcification in T1DM, *eGDR* estimated glucose disposal rate, *IS* insulin sensitivity score, *eIS* estimated insulin sensitivity, *WHR* waist to hip ratio, *TG* Triglycerides, *DBP* Diastolic Blood Pressure

Methods

This is an exploratory meta-analysis and follows the PRISMA (Preferred Reporting of Systematic Review and Meta-analysis) guidelines.

Search strategy, and Inclusion and exclusion criteria

Two authors independently searched for the relevant keywords in three databases (PubMed, SCOPUS, Web of Science) for identification of research articles related to MetS and IR in children, adolescents, and young adults with T1DM. The search was performed till May 5, 2023. The articles were from 1982 to 2023. The search for the relevant keywords was as follows.

((("Type 1 Diabetes" OR "IDDM" OR "insulin dependent diabetes" OR "T1DM") AND ("insulin resistance" OR "IR" OR "Metabolic syndrome" OR "MetS" OR "insulin sensitivity" OR "IS")) AND ("Molecular markers" OR "markers" OR "Biological markers" OR "Clinical markers" OR "gene expression markers")) AND ("Paediatric" OR "child" OR "children" OR "adolescent" OR "adolescence" OR "young adult").

The search was limited to peer reviewed English articles. Only original research articles were included for this review. Studies that had type 1 diabetes population with the age group < 25yrs were retained. The studies were then imported to a Rayyan software for screening and removal of duplicates [42]. Studies using animal models, cell lines, and organ tissue samples were excluded. Studies including children with complications associated with diabetes and on medication other than insulin therapy were excluded.

Selection of studies and data extraction

We segregated the studies based on presence or absence of MetS and IR in the T1DM population. The studies that provide markers for such conditions, either standard (insulin dose, eGDR for IR, IDF criteria for MetS) or surrogate (body mass index: BMI, WC etc.), were included in this review. Meta-analysis was performed only if multiple studies with similar parameters were available. Other studies were utilized for descriptive review. Parameters such as duration of diabetes, insulin dosage, HbA1c, and lipid profile were assessed in each study. The sample size, mean, and standard deviation (sd) for each parameter were recorded accordingly. If median and interquartile range were provided they were converted to estimated mean and variance depending on sample size [43]. Author names, publication year, ethnicity, and gender details of the population were also recorded for the studies that were part of the systematic review (Table 3).

Statistical analysis and evaluation

Meta-analysis was performed when two or more studies reported mean, standard deviation, and sample size. Metaphor package was applied for the analysis [69]. Standard Mean Difference (SMD) was calculated using R (version 4.1.1). We calculated the effect size (ES) in terms of hedges g that corrects for the sample size providing unbiased adjusted ES. Random effects model (REM) was used for quantitative meta-analysis. A forest plot was used to visualize summary of results [70]. Chi-squared test was used to measure heterogeneity (p val < 0.1). The I^2 statistic was used to estimate if the heterogeneity was considerable ($I^2 > 40\%$) [71]. The strength of relationship between parameters and traits was estimated based on the effect size (0–0.2: no effect; 0.2–0.5: small; 0.5–0.8: moderate; 0.8–1: large; > 1: very large effect) [72].

Assessment of Sensitivity and publication bias

Funnel plots were used for visualization of publication bias [73]. The pooled results were analysed for their sensitivity by sequential removal of individual studies and their effect on heterogeneity.

Results

Identification of studies for diagnostic markers of MetS and IR

We identified 67 research articles on PubMed, 930 on SCOPUS, and 88 on Web of Science by searching keywords in titles and abstracts. After applying the filters for language and exclusion criteria, 66, 739, and 86 articles were retained. Manual search provided 3 additional studies. These articles were then imported in Rayyan [42]. In this software 78 duplicate articles were removed and 816 unique original research articles were retained. Based on the screening of abstracts and titles, 743 articles were omitted. Full text scrutiny identified 73 research articles, and 30 research articles were retained based on inclusion and exclusion criteria (Fig. 1).

The general nature of these research articles is mentioned in Table 3. All were observational studies with a cross-sectional or longitudinal design. The data in the studies was

Table 3 Characteristic of studies included in the systematic review

Sr. no	Author name/year	Type of Study	Ethnicity	Case (M/F)-Control (M/F) or Cohort(M/F)	Comparative groups	Markers for MetS/ IR	Age (yrs)
1	Nadeau et al. 2010 [44]	C,P	Black (8.3%), Hispanic (8.3%), White(75%), other(8.3%)	Case (6/6), Control (6/6)	Children without diabetes	HEC with VO2 peak ($r=0.61$, $p=0.007$)	12–19
2	D. Dabelea et al. 2011 [31]	C,P	Non-hispanic whites, Hispanics, African American)	Case (26/43) Control (8/17)	Children with T2DM	HEC with IS score (SEARCH) ($r=0.65$, $p=0.0001$)	12–19
3	D. Dabelea et al. 2011[45]*	C,P	67.9% Non-Hispanic whites (NHWs), 13.3% Hispanics, 13.4% African Americans (AAs), 4.1% Asian/Pacific Islanders (APIs), and 1.3% American Indians (AIs)	Case(218/228), Control(646/602)	Children with T2DM	IS score by SEARCH (IR < 8.15)	< 20
4	Davis et al. 2012 [46]	C,P	NA	Case (18/12), Control (8/6)	Children without diabetes	Higher insulin dose, high HbA1c	0–18
5	Rathsman et al. 2012 [47]	C,P	Caucasian	Case (12/8), Control(7/13)	Children without diabetes	MetS by NCEP ATP III, WHO, IDF HEC(Si) to cIMT: $r=0.22$	14–20
6	Narges Safai et al., 2015 [48]	L, R	18 immigrants, 12 unreported ethnicity, others Danish origin	Case (255/227), Control (266/231)	Children without diabetes	Adiponectin, leptin (increase in both increases insulin sensitivity)	0–15
7	Chan et al. 2017 [49]	C,P	NA	Case (46/54), Control (11/31)	T2D	HEC with AST & cholesterol ($r=-0.21$, $p<0.05$), BMI% ($r=-0.40$, $p<0.001$), TG($r=-0.34$, $p<0.001$), WC($r=-0.45$, $p<0.001$)	12–19
8	Cree-Green et al. 2018 [50]	C,P	T1DM are more Caucasian	Case (16/19), Control(6/16)	T2D	HEC with FFA ($r=-0.46$, $p=0.005$), Leptin ($r=-0.44$, $p=0.008$)	14–17
9	E Gourgari 2020 [51]*	L,P	Non-Hispanic White 72%, other 28%	Case(196/180), Control(55/102)	T2D	IS score by SEARCH (ISS > 8.15 included for T1DM)	18 ± 4.1
10	Hamed et al. 2021 [52]	L,P	NA	Case (3/4), Control(22/37)	T2D	Acanthosis nigricans, family history of DM, c-peptide, HbA1c	9–12

Table 3 (continued)

Sr. no	Author name/year	Type of Study	Ethnicity	Case (M/F)-Control (M/F) or Cohort(M/F)	Comparative groups	Markers for MetS/ IR	Age (yrs)
11	Calcaterra et al. 2021 [53]	C,P	NA	Case (0/14), Control (0/18), Control (0/20)	Children without diabetes	eGDR = 21.158 + (−0.09 * WC) + −3.407 x (HTN) + −0.551 x (HbA1c) eGDR < 8.77 mg kg^{-1} min^{-1} low adiponectin and high kisspeptin in IR	12.1 ± 4.1
12	Monika Grabia et al. 2021 [11]	C,P	Polish	Case (33/27), Control(44/16)	Children having T1DM with MetS vs children without MetS	MetS by IDF, NCEP ATP III, WHO, eGDR by 21.158 − (0.090 × WC) − (3.407 × HT) − (0.551 × HbA1c) ≤8 mg/kg/min (for MetS diagnosis)	10–17
13	Stone et al. 2006 [54]	L,R	NA	Cohort(161)	NA	Higher BMI, higher insulin dose, DHEAS	13.7 ± 2.2
14	Szadkowska et al. 2008 [8]	C,P	NA	Cohort (112/90)	Correlation to Lipid parameters and adiposity markers	HEC (M_{lbm}) with lipid [Cholesterol ($r = -0.18$, $p = 0.012$), HDL ($r = 0.15$, $p = 0.035$), LDL ($r = -0.22$, $p = 0.002$), TG ($r = -0.32$, $p < 0.001$)], SBP($r = -0.15$, $p = 0.029$), Adiposity [BMI($r = -0.29$, $p < 0.001$), WC($r = -0.35$, $p < 0.001$), Tricep ($r = -0.16$, $p = 0.027$), Subscapular ($r = -0.22$, $p = 0.002$), Body fat($r = -0.19$, $p = 0.006$)]	> 8–< 18
15	Mazumder et al. 2009 [55]	C,P	Asian	Cohort (30/28)	NA	Increased insulin dose, acanthosis nigricans, increased body fat	16.5 ± 2.3
16	Girgis, Scalley, and park 2012 [56]	C,P	NA	Cohort (29/32)	girls vs boys	eGDR = 24.31–12.2 x (WHR)-3.29 x (HTN)-0.57 × HbA1c obese vs non-obese T1DM (eGDR 6.5 ± 1.6 8.6 ± 1.8 mg/ kg min respectively, $p = 0.29$)	16–25

Table 3 (continued)

Sr. no	Author name/year	Type of Study	Ethnicity	Case (M/F)-Control (M/F) or Cohort(M/F)	Comparative groups	Markers for MetS/ IR	Age (yrs)
17	G. Valerio 2012 [57]	C,P	Caucasian of Italian origin	Cohort (219/193)	Children having T1DM with MetS vs children without MetS	IDF for MetS, logistic regression: [insulin dose (OR = 1.04, 95% CI 1–1.07, $p = 0.025$),WHR (OR = 11.03, 95% CI 5.23–23.24, $p = < 0.001$)	16–19
18	Maya jesic et al., 2013 [58]	C,P	NA	Cohort (51/49)	Normo vs micro albuminuric	High insulin dose, hypercholesterolemia, DHEAS	11–19.4
19	Lecaire and Palta 2015 [59]	L,P	White (97%)	Cohort (99/88)	Follow-up study	Insulin dose, Adiponectin	11.2(6.8)
20	Cedillo et al. 2015 [60]	C,P	NA	Cohort (155/108)	Children with central obesity vs children with non-central obese	BMI > 95th percentile for obesity, WHtR > 0.5 for central obesity (obesity driven IR)	< 19
21	Siraz et al. 2017 [61]	C,P	NA	Cohort (40/40)	Children with NAFLD vs children without NAFLD (represents peripheral IR)	Fetuin A (AUC = 0.672, 95% CI 0.558–0.773; $p = 0.022$), higher ALT	9–17
22	Bjornstad et al.2017 [62]	C,P	NA	Cohort (20/21)	leptin tertiles	HEC, leptin tertiles related to VO2 peak independent of IS	12–21
23	Sevaliev et al. 2019 [63]	C,R	84% Jewish, 16% Arab	Cohort (48/48)	girls vs boys	Children with high BMI showed component of MetS such as high SBP, low HDL compared to children having normal BMI	5–21
24	Soliman, Mosaad, and Ibrahim 2019 [15]	C,P	NA	Cohort (77/83)	Children having T1DM with MetS vs children without MetS	IDF for MetS, eGDR correlates with Age($r = -0.27$, $p = 0.001$), duration of diabetes($r = -0.18$, $p = 0.02$), weight($r = -0.35$, $p < 0.001$), BMI($r = -0.27$, $p = 0.001$), SBP($r = -0.48$, $p < 0.001$), DBP($r = -0.4$, $p < 0.001$), WC($r = -0.5$, $p < 0.001$), HbA1c($r = -0.69$, $p < 0.001$), LDL & TG ($r = -0.18$, $p = 0.02$), cholesterol ($r = -0.16$, $p = 0.04$)	13.38 ± 2.17

Table 3 (continued)

Sr. no	Author name/year	Type of Study	Ethnicity	Case (M/F)-Control (M/F) or Cohort(M/F)	Comparative groups	Markers for MetS/ IR	Age (yrs)
25	Marigliano et al. 2020 [64]	C,P	Caucasian	Cohort (8/7)	NA (but lean population)	eGDR with exogenous CHOs oxidized ($r=0.7$, $p<0.02$), differential enrichment of C12/C13 in the expired breath test ($r=0.59$, $p<0.05$) ISS with exogenous CHOs oxidized($r=0.61$, $p<0.05$), differential enrichment of C12/C13 in the expired breath test($r=0.62$, $p<0.05$)	8–14
26	Nishtala et al. 2020 [65]	C,R	Caucasian, African, Caribbean, South Asian, others	Cohort (108/67)	eGDR tertiles	$eGDR_{BMI}$ tertiles correlated with clinical parameter. Low eGDR had high cholesterol and TG	22 ± 1.6
27	Koken et al. 2020 [16]	L,P	NA	Cohort (104/96)	Children having T1DM with MetS vs children without MetS	IDF, WHO, NCEP ATP III WC, TG significantly high ($p<0.001$) and LDL also high ($p=0.05$) in MetS positive	8–18
28	Morandi et al. 2021 [66]	C,P	NA	Cohort (82/72)	girls vs boys	CACTI(eIS) for IR D6D activity with eIS ($r=-0.32$, $p=6.6\times10^{-5}$), TG($r=0.24$, $p=0.003$)	15.5–18.9
29	Gomes et al. 2022 [67]*	C,P	Caucasians 48%	Cohort (183/184)	overweight vs non-overweight	IDF for MetS for 10 to 16, and IDF adult for above 16yrs	10–19
30	Shah et al. 2023 [68]	C,P	Asian	Cohort(38/41)	ALR < 1 vs ALR > 1	Adiponectin to Leptin ratio as MetS marker	10–21

C cross-sectional, *L* longitudinal, *P* prospective, *R* retrospective, *ISS* insulin sensitivity score, *SI* insulin sensitivity, *eGDR* estimated glucose disposal rate, *GIR* glucose infusion rate, *ALT* alanine amino transferase, *eIS* estimated insulin sensitivity, *ALR* Adiponectin to Leptin ratios

*Multicentre study. All other are single centre studies

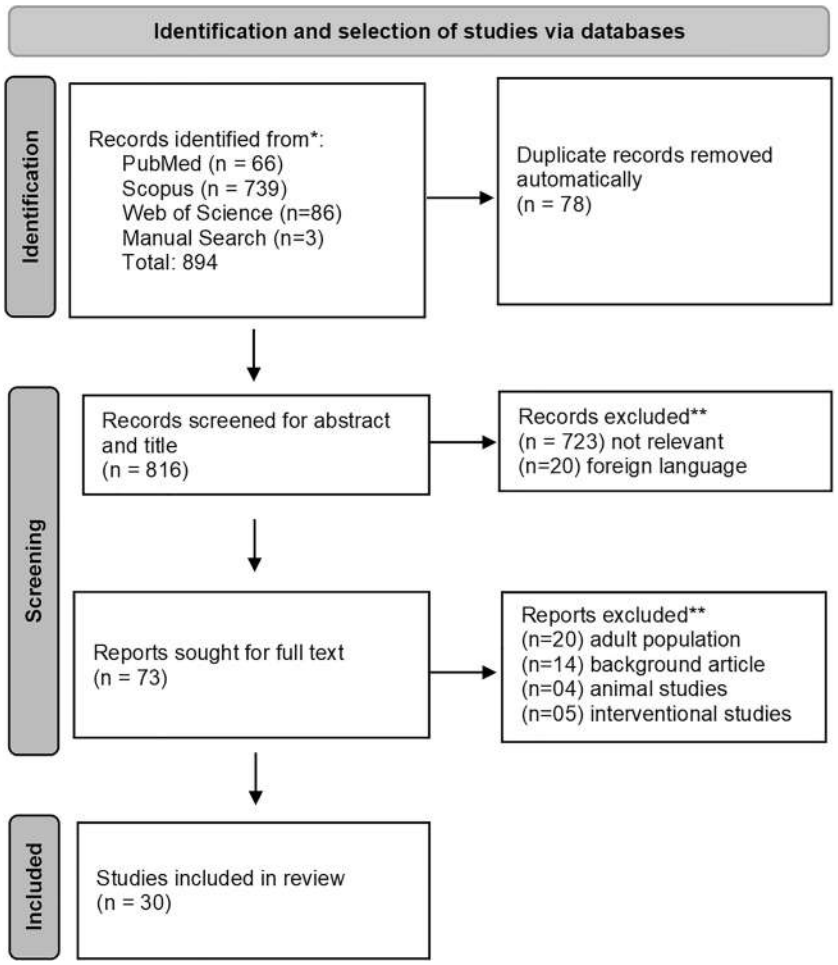

Fig. 1 PRISMA flow diagram for illustration of the identification and screening process. Search terms were used to compile the results in different databases and imported together in software Rayyan for duplicates removal and screening

either prospectively collected or used retrospectively from registries and hospitals.

Qualitative summary and characteristics of studies

As mentioned earlier, we limited our search to observational studies. There were a total of 30 studies with standard and surrogate markers of MetS and IR in T1DM. 12 studies were based on case–control and 18 studies were cohort based. Six studies provided novel markers for IR whereas, 24 studies used existing parameters for IR and MetS. Information about ethnicity was not available for 15 studies (Table 3). Five of the 30 studies compared children with T1DM with children whereas, another 5 studies compared children with T1DM to children with T2DM. Four studies assessed MetS in children with T1DM by grouping them according to IDF criteria. The grouping of studies for IR was difficult as only two studies have classified the children with T1DM on the basis of IR indices (eGDR) [45, 65] (Table 4).

Assessment of markers for MetS in T1DM Four studies out of thirty have grouped T1DM children as being MetS positive and MetS negative (Table 4). The parameters such as units of insulin, HbA1c, WC and lipid profile were selected for our meta-analysis. Summary statistics for fasting glucose and hypertension were not available.

Random Effect Model (REM) was used where, WC ($d = 1.34$, [95% CI: 0.79–1.90]) and TG ($d = 0.85$, [95% CI: 0.14–1.55]) showed significantly large effect size whereas, HbA1c ($d = 0.75$, [95% CI: −0.20–1.71]), and LDL ($d = 0.73$, [95% CI: 0.15–1.32]) showed a moderate effect on MetS. The effect size was significant for LDL but not for HbA1c. On the other hand, HDL ($d = 0.37$, [95% CI: −0.65–−0.10]) showed a significantly small negative effect. Units of insulin dosage ($d = 0.17$, [95% CI: −0.06–0.4]) also showed no significant effect on MetS (Fig. 2).

Assessment of publication bias

No heterogeneity was observed for insulin dose and HDL, however; a heterogeneity was observed for HbA1c, LDL, TG, and WC in the identified datasets (Fig. 2). Since, the latter showed a significant heterogeneity, we decided to

Table 4 Studies that have categorized children with T1DM based on presence or absence of metabolic syndrome and insulin resistance

no	Author	Sample number	Parameters in the study	Origin/other
A. Studies based on the presence or absence of metabolic syndrome				
1	Giuliana Valerio et al., 2012 [57]	411 (39/372)	Insulin dose(U/kg/day), WC (cm), BMI(kg/m^2), W/H ratio, HbA1c(%)	Caucasian of Italian origin, > 1 yr of duration of diabetes
2	M Soliman et al., 2021 [52]	160 (21/139)	Duration of diabetes(yr), insulin dose(U/kg/day), HbA1C, weight, height, BMI(%), SBP(mmHg), DBP(mmHg), WC(cm), TG(mmHg),	Afrocentric ethnicity, 1yrs or > 1 yr diabetes duration
3	OY Koken et al., 2020 [16]	200 (21/179)	Duration of diabetes(yr), family history, insulin dose, Acanthosis, WC(cm), HbA1c(%), TG(mg/dl), HDL(mg/dl), LDL(mg/dl)	Turkish, 4.6 + 3.3yrs of diabetes duration
4	Monika Grabia et al., 2022 [74]	60 (20/40)	WC(cm), W/H ratio, WHtR, BMI (kg/m^2), HbA1C(%), eGDR(mg/kg/min), TC(mg/dl), LDL(mg/dl), HDL(mg/dl), TG(mg/dl), SBP(mmhg), DBP(mmhg)	Polish, 2-7yrs of diabetes duration
B. Studies based on the presence or absence of insulin resistance				
1	Nishtala R et al., 2020 [65]	175 (eGDR < 7.34 = 58, eGDR 7.34–8.92 = 56, eGDR > 8.93 = 61))	Age, sex, ethnicity, duration of diabetes, BMI, HbA1c, eGDR, eGFR, SBP, DBP, TC, HDL, LDL, TG	Mixed(Caucasian 81.7%, African carribean2.3%, south Asian 6.3%, other 2.3%)
2	Dabelea et al., 2011 [45]	1694 (IS = 1248, IR = 446)	Onset age, duration of diabetes, family history, IS score, FCP, GADA titres, BMI as z score, WC	67.9% Non-Hispanic whites (NHWs), 13.3% Hispanics, 13.4% African Americans (AAs), 4.1% Asian/ Pacific Islanders (APIs), and 1.3% American Indians (AIs)

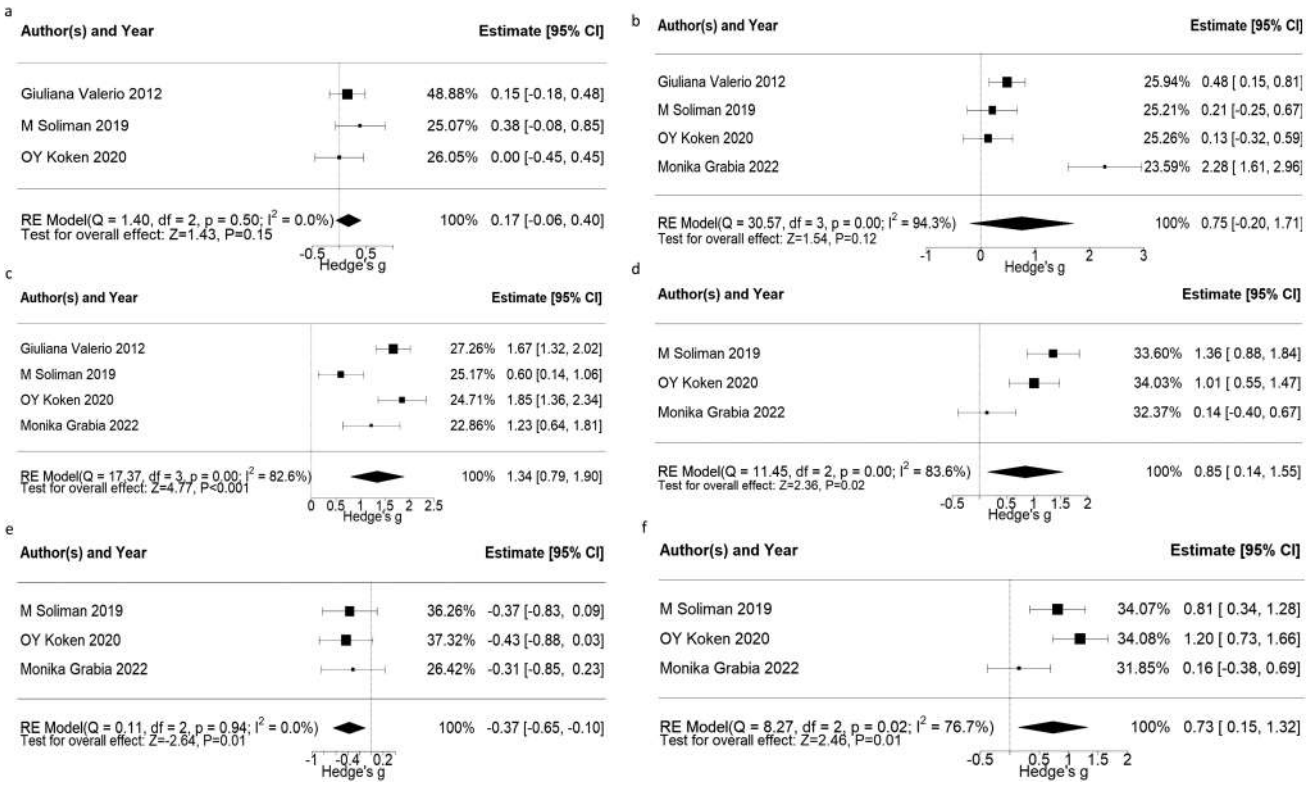

Fig. 2 Comparison between parameters of metabolic positive and metabolic negative groups of type 1 diabetes. (**a**) Insulin dosage, (**b**)HbA1c, (**c**)waist circumference, (**d**)Triglycerides, (**e**) High density lipoprotein, (**f**) Low density lipoprotein

assess the publication bias. A funnel plot analysis was performed for all the markers mentioned above (Supplementary Fig. 1). HDL and the units of insulin did not show any outliers. The publication bias was assessed for the remaining parameters such as HbA1c, WC, TG, and LDL by sequential removal of each study. The study by Monika Grabia et al. 2022 strongly contributed to the heterogeneity for HbA1c, TG, and LDL. Removal of this dataset removed the heterogeneity and improved the effect size of TG (from 0.85 to 1.18) and LDL (from 0.73 to 1). The effect size of HbA1c (from 0.75 to 0.32) on the other hand, reduced. In case of WC, strong heterogeneity was contributed by the study by Soliman et al. 2019. Removal of this dataset improved the effect size of WC (from 1.34 to 1.63). The possible sources of heterogeneity are discussed later. In summary, TG, LDL, and WC seem to have a significantly large effect on MetS (Supplementary Fig. 2).

Assessment of markers for IR in T1DM Out of the 30 studies, only two studies had grouped the participants based on presence or absence of IR [45, 65]. In both these studies the measurement of IR was performed by using eGDR. However, Nisthala et al., 2020, divided the children having T1DM by $eGDR_{BMI}$ and the association of $eGDR_{BMI}$ with different clinical parameters was observed. The study suggested that the population in lower quartiles of $eGDR_{BMI}$ had significantly higher levels of total cholesterol and triglycerides. Dabelea et al., 2011 attempted to segregate the population of children with T1DM and T2DM based on eGDR. The study found stronger association of IR in children with T2DM than in T1DM. The parameters to calculate eGDR and the study design were not consistent between these two studies (Table 4). As a result, we provide a descriptive review of other markers for IR. Some of the markers that include Volume of Oxygen uptake during peak exercise ($VO2_{peak}$), Free Fatty Acid (FFA), Leptin, cIMT (carotid intima media thickness), have been validated using HEC. A few others markers have been validated using indices such as eGDR, SEARCH, and CACTI (Table 3).

Quantitative markers frequently used by clinicians include measurement of insulin dosage in combination with HbA1c [46], central obesity [54], and body fat [8]. Along with HbA1c, family history for T2DM is an important parameter. Central obesity measured by waist to height ratio > 0.5 and BMI > 95 percentile are also suggested parameters for IR [60]. Body fat estimated by thickness of triceps and subscapular skin fold have been used to predict body fat [8]. A qualitative marker: acanthosis nigricans is also used as an indicator of IR; however, it is more related to obesity than IR [45, 52, 53, 55].

Some of the novel quantitative markers such as adiponectin, leptin, fetuin A, and kisspeptin are being investigated for the assessment of IR. A longitudinal study in T1DM children suggested that levels of adiponectin, (a hormone produced by adipocytes with a role in insulin sensitization) were strongly related to WC and insulin dose in 20 yr old adults with T1DM [59]. Adiponectin and leptin (another hormone produced by adipose tissue involved in maintenance of normal body weight), both have been studied in association with IR [48]. It has recently been suggested that leptin may act as a potential biomarker for the detection of IR in T2DM. In case of T1DM, the association of leptin with IR is not very well studied. However, a few reports suggest that fluctuations in leptin levels are observed in children and adolescents with T1DM [48, 62]. Increase in fetuin A, a hepatokine and an adipokine, is associated with IR and obesity. In T1DM, this association was limited to glycemic levels and as a risk predictor for complications of diabetes. Further studies to assess the role of fetuin A in IR are needed. Another hormone, Kisspeptin (produced in the hypothalamus) inversely associates with adiponectin levels and in turn, to insulin sensitivity [75]. However, the association was only studied in reproductive age female population. Further studies will be required to conclude kisspeptin as a marker for IR. Two studies have shown an association of IR markers (increased insulin dose, increased BMI and, increased Dehydroepiandrosterone sulphate (DHEAS) with increased micro-albuminuria [54, 58]. The DHEAS is a precursor for sex hormones and is known to act as an insulin sensitizer. $VO2_{peak}$ which is a measure of cardiovascular and skeletal muscle oxidative function shows a significant moderate positive correlation with HEC (reduced GDR by HEC indicate IR) [44].

Other less studied novel indicators include carbohydrate (CHO) oxidation and Delta 6 desaturase (D6D) activity. The CHO oxidation which estimates the capacity to oxidise a meal in the form of differential 13C/12C enrichment in the expired air using flow isotope mass spectrometry, has been associated with IR. The CHO oxidation showed a moderate correlation with eGDR in T1DM [64]. A high activity of D6D, a rate limiting enzyme in production of long chain Poly Unsaturated Fatty Acids (PUFA) has been associated with decreased insulin sensitivity therefore, increased activity of D6D has been suggested to be a strong marker for IR in T1DM adolescents [66] and non-diabetic adults [76]. All the novel quantitative markers are still under investigation and are not part of routine clinical applications.

Discussion

Metabolic syndrome (MetS) and Insulin resistance (IR) in combination and independently can be the risk factors for CVD. Usually surrogate markers are used for the diagnosis of MetS and IR in children with T1DM. We performed a systematic review and a meta-analysis to study the effect size of the parameters for the diagnosis of MetS in children with T1DM. Participants with T1DM aged < 25yrs were included due to the lack of experimental evidence for the cutoffs in this age group. To focus specifically on metabolic syndrome, we excluded participants with complications related to T1DM or those taking medication other than insulin therapy. Inconsistency in measurement methods made it challenging to perform a similar meta-analysis for IR (Table 4).

In our meta-analysis, insulin dosage and HbA1c showed low effect size suggesting that the MetS appears independent of glycemic condition in children with T1DM (Fig. 2a, b). WC was strongly associated (with large effect size) with MetS in T1DM (Fig. 2c). Since, all four studies made use of the IDF criteria which require central obesity as a mandatory component for the assessment of MetS, this association was expected. However, this association was observed with a considerable heterogeneity that was contributed by Soliman et al. (2019). The study cohort was from Egypt and the population has been shown to have a different cut-off for WC for obesity [77]. Removal of this study removed the heterogeneity and increased the effect size (Supplementary Fig. 2). Our results fall in line with previous studies where WC predicted MetS in adults with T1DM [78] and was significantly associated with MetS in children who did not have diabetes [79].

Increased TG and LDL were also associated (large and moderate effect size respectively) with MetS in children with T1DM (Fig. 2f). The source heterogeneity contributed to this association may have been from the attempt to convert median and interquartile range provided by Monika Grabia et al. (2021) to mean and standard deviation [43]. The omission of this study did not alter the effect size for TG whereas, effect size for LDL improved from moderate to large (Supplementary Fig. 2). TG are already a part of IDF criteria and together with WC provide a better diagnostic efficiency for MetS [80]. Considering that LDL is not a part of the IDF criteria for MetS, the strong association of LDL with MetS is noteworthy. Increased LDL is suggested to be a risk factor for CVD [81]. Significantly increased LDL was observed in children who do not have diabetes but, had predisposition to MetS [82]. Moreover, reduction in LDL levels are suggested as a treatment strategy by the IDF [83]. This reflects the significance of LDL in MetS. Therefore, increased LDL can be used as one of the parameters to screen for MetS in children with T1DM. However, LDL alone might be an insufficient indicator and may thus be used along with other parameters in the assessment of MetS [84]. HDL is one of the parameters proposed by the IDF, WHO, and NCEP III to screen MetS. HDL is known to have a negative association with MetS

which was reflected in our analysis. All datasets showed homogeneity for HDL; however, the cumulative effect size of HDL was moderate. Other than lipid profile, some inflammatory markers such as adiponectin and leptin are under investigation for their association with cardiometabolic risk in children with MetS [68].

For IR, we came across only two studies where young people having T1DM were classified based on presence or absence of IR. Diverse designs and varying parameters to test IR made the compilation of studies difficult. We came across a large number of non-invasive and invasive parameters used to assess IR in T1DM. Most of them are quantitative in nature (Supplementary Table 2). Routinely used quantitative measures include BMI and waist-to-height ratio. Increased BMI was one of the components for IR detection. However, with recent observations of IR in lean children with T1DM [46], it has become evident that people especially of Asian ethnicity may follow a 'thin fat' phenotype with low normal BMI, and high percent fat [55]. Therefore, waist-to-height ratio may be a better marker than BMI for IR detection. Increased dose of insulin is observed in children having T1DM with IR. Insulin dosage may vary depending on the meal type, physical activity etc. Thus, insulin dose may not represent the accurate status of IR in children with T1DM. A qualitative marker-Acanthosis Nigricans (AN) may be observed as a result of abnormal proliferation of keratinocytes due to excessive binding of insulin to insulin like growth factor receptor rather than insulin receptor [85]. Acanthosis is observed to be associated with obesity more than IR.

Among the novel markers, breath test and cIMT offer least invasive methods for detection of IR. The breath test assesses the capacity to oxidize exogenous carbohydrates which directly correlate with eGDR and ISS significantly. This is presented by enriched C12/13 in expired breath [64]. This method being non-invasive can be more applicable to large paediatric cohorts. The cIMT (carotid intima media thickness), an early sign of atherosclerosis correlates moderately with insulin sensitivity is not a direct measure for IR. Its use in assessing the cardiovascular risk is limited. Moreover, the test is expensive and difficult to add in to a routine check-up.

Investigations of hormones involved in the pathogenesis of IR could provide valuable insights. Most of these hormones are novel and under investigation. These hormones actively participate in metabolic regulation and include adiponectin, leptin, fetuin A, kisspeptin etc. Adiponectin an insulin sensitizer produced by adipose tissue, involved in regulation of gluconeogenesis is suggested to be reduced in participants with T1DM [48] (Table 3). Adiponectin showed a strong discriminatory power for detection of IR in adolescents who did not have diabetes [86, 87]. Leptin, an appetite suppressing hormone, plays a role in energy balance by reducing energy uptake and increasing energy expenditure. Similar to adiponectin, leptin it is produced by white adipose tissues and shows negative correlation with insulin sensitivity. The evaluation of the ratio of both these hormones has been limited in adolescents who do not have diabetes [88]. Fetuin A, an inhibitor of insulin receptor tyrosine kinase activity is a suggested marker for IR in adolescents with no signs of diabetes [89]. Kisspeptin was observed to be higher in people with IR [75]. All these hormones lack assessment of their role as marker in children with T1DM and validation against HEC. An understanding of the pattern of these hormones with respect to IR provides a window for development of novel indices for the diagnosis of IR.

Other markers that are least understood and are under investigation include reduced D6D activity. Erythrocyte D6D activity has been suggested to be a strong marker of IR in T1DM [66]. D6D is a desaturase enzyme that introduces a double bond in a specific position of long chain fatty acids. Reduced activity of D6D can interfere with the fatty acid composition. The detailed explanation of this reduced activity is beyond the scope of our review. However, to consider D6D as an IR marker, more detailed studies are required.

Strengths and limitations of the study

To the best of our knowledge, this is the first systematic review and meta-analysis for assessment of surrogate markers for MetS and a systematic review for IR in children with T1DM. However, for the IR, the studies are reported in different forms of indices which made it difficult for us to compile them for the assessment of IR markers. Also, this systematic review could not assess the effect of age and pubertal status on the accuracy of markers of MetS and IR. The number of studies available for meta-analysis are very small hence, with increasing reports there are chances that the results may improve in future.

Conclusion

From the results it can be concluded that in the children with T1DM, markers of glycemic levels are not associated with MetS. Other than TG and HDL, LDL may also be considered in the diagnostic criteria for MetS. A combination of WC and TG may increase the efficacy of MetS diagnosis in paediatric population living with T1DM. Many novel markers currently under investigation for the diagnosis of IR need evaluation against HEC. These markers may be used in combination to increase the accuracy of IR diagnosis.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13410-023-01284-3.

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Author's contribution SBK and VK performed the systematic literature search. SBK performed the statistical analysis. SBK and SPK wrote the manuscript. AK and SPK contributed to conceptual design of the study.

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Data Availability No new data generated. Data sharing not applicable.

Code availability https://github.com/macdlab/2023_SK_T1DM_metanalysis

Declarations

Systematic review registration PROSPERO CRD42023418954.

Ethics declaration No ethical approval was needed as the data was collected from previous published studies in which the informed consent was obtained by primary investigators.

Conflict of interest The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Bio-demographical determinants of diabetes among women in reproductive age group (15–49) in India: Evidence from National Family Health Survey (NFHS) of India, 2019–2021

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Abstract

Objective Diabetes is a non-communicable disease, and the prevalence of diabetes is higher in low and middle-income countries. In India, diabetes prevalence has been observed, with some regional variations across the states. This study analyses the current scenario of diabetes in India among women of the reproductive age group between 15 to 49 years.

Methods For conducting this study, data were gathered from the fifth round of the National Family Health Survey (2019–2021). It is a two-stage cross-sectional stratified sampling survey that employs the probability proportional to size methodology. A total of 6,59,010 individual reproductive-age women have been sampled for this study. Data were analyzed using the Stata version 14 software. A binary logistic model was carried out to know the relationships between diabetes and various socioeconomic and demographic variables. In addition, the adjusted odds ratio was reported with a 95% confidence interval.

Results The result shows that about 1.65% of reproductive age group women in India are diabetic with the highest in Goa (4.09%) and the lowest in Nagaland (0.81%). Further, in urban areas, the women's diabetes rate is 16% higher than in the rural areas. Besides, diabetes is strongly correlated with obese reproductive age-group women who are above 35 years and reside in urban areas with higher socioeconomic status.

Conclusion This study suggests that there is an urgent need for frequent monitoring of glycated haemoglobin (HbA1c). Besides, a spatially-optimized target-oriented policy framework is needed instead of a comprehensive national policy to tackle diabetes problems in the country.

Keywords Diabetes · Non-communicable disease · Binary logistic model · NFHS-5 · Women · India

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Introduction

Diabetes is a non-communicable disease (NCD). It is the primary cause of death and low life expectancy [1] and a major public health concern worldwide, particularly in developing countries. The rate of diabetes increases sharply with economic development, nutritional transition, increasing sedentary lifestyle, and prevalence of obesity [2]. Diabetes was responsible for 6.7 million deaths in 2021. It is estimated that one person dies of diabetes every five seconds worldwide [3]. According to WHO, diabetes was the leading cause of death globally in 2019, with an estimated 1.5 million deaths. The prevalence of diabetes is expected to rise from 2.8% (171 million) in 2000 to 4.8% (366 million) in 2030. Further, population ageing, rapid urbanization, changing lifestyles, unhealthy dietary habits, and physical inactivity are the major causes of diabetes [4, 5]. Although diabetes is a common problem across the World, it is more

pronounced in the developing countries of South-Asia, especially in low and middle-income countries (LMCs) [3, 6, 7]. The early detection of diabetes can reduce the disease burden and improve the quality of life. Due to the non-reversible nature of the disease, raising awareness, treatment, and control (ATC) is key to reducing the burden of diabetes [8].

The literature evaluation indicates that little study has been done to fully examine the connection between diabetes and socioeconomic factors (SEFs) in India [9–11]. The prevalence of Diabetes is an emerging health concern across the geographical areas and socio-demographic groups in India [12]. Over 74 million people in India have diabetes. In addition, diabetes affects both sexes equally; however, men (2.63%) are more affected than women (2.35%) [3]. Compare to older women, older men have a higher prevalence of type 2 diabetes. Besides, 14.6% of men and 9.1% of women have type 2 diabetes mellitus (T2DM) in India, respectively [13]. It was noticed that women having higher socioeconomic status have higher risks of diabetes than women having low socioeconomic status [14]. Diabetes is more pronounced in urban areas than in rural. Different study reveals that being overweight, obese, and high living standard is positively related to diabetes and these are very high in urban areas [15]. And diabetes is strongly correlated with obese reproductive age-group women who are above 35 years and residing in urban areas with higher socioeconomic status. The prevalence of diabetes is higher among the states and union territories (UTs) which are in their advanced stage of demographic transition and have a higher proportion of the elderly population [16].

This study assesses the current status of diabetes, and finds out how various bio-demographic factors are correlated with diabetes among reproductive women in India. The review of the literature revealed that very few studies have been conducted to examine the present scenario of diabetes among the women of the reproductive age-group based on the fifth round of the National Family Health Survey (NFHS-5), 2019–2021. Therefore, a systematic study is needed to examine the present status of diabetes among the mentioned cohort. This work is an endeavour to fill the gaps in the existing literature.

Materials and methods

Data source

The data for this study was collected from the fifth round of NFHS. It is a two-stage cross-sectional stratified sampling survey using the probability proportional to size (PPS), which was conducted from 2019 to 2021 in India. It uses primary sampling units (PSUs) at the village level and census enumeration blocks (CEBs) for non-slum or urban areas. It also provides information about the socioeconomic condition, demography, and health of women, men, couples, and children in India. For this study, individual data on women were collected from the fifth round of the NFHS of India. The NFHS-5 provides a nationally representative sample of individual reproductive-age women. The survey was conducted across 707 districts in 28 states and 8 union territories of India. A total of 7,24,115 women were successfully interviewed. In this study, however, we only considered women who responded to all variables. All the variables used in our study were answered by only 6,59,010 respondents, while 65,105 respondents didn't respond to all the questions; therefore, we deliberately eliminated their answers.

Study variables description

A quantitative method was employed to conduct this study. A detailed description is given below.

Independent variable

We conducted the study to determine how various bio-demographic factors contribute to the prevalence of diabetes among reproductive-age women in India. The main variables of the study were age group, marital status, caste, religion, place of residence, education, wealth index, parity, family size, Body Mass Index (BMI), and waist circumference. The age group variable was recoded into three different categories:15–24, 24–34, and ≥ 35. The marital status of women was classified into three categories: married, unmarried, and others. Divorced and widowed were separate categories, recorded and renamed as others. The remaining variables such as caste, religion, place of residence, education, and calculated wealth index are already provided in the NFHS-5 dataset. The parity of women was classified into four groups: 0, 1, 2, and > 2. Family size was included as an independent variable, which was categorized and recoded into three groups: below 4, 4 to 7, and > 7. A BMI was measured based on the booking weight (kilograms) and height (metres). To maintain the accuracy of our calculation, we removed negative and very high values (≥ 9096 kg/m^2) of BMI from the dataset. For BMI, we classified the values into four groups: underweight, normal, overweight, and obese, and generated a new variable. Based on the revised consensus guidelines for India, < 18.49 kg/m^2 coded as 1 (underweight), 18.5 to 22.9 kg/m^2 coded as 2 (normal weight or lean BMI), 23.0–24.9 kg/m^2 coded as 3 (overweight), and ≥ 25 kg/m^2 coded as 4 (obese), [17, 18]. Likewise, waist circumference was categorized into two groups: < 80 cm coded as 1 (low risk) and > 80 cm coded as 2 (high risk) [19, 20].

Dependent variable

The primary outcome variable for this study is diabetes among women of reproductive age (15–49 years). The NFHS-5 in India follows a standardized protocol to measure diabetes in the population, which involves measuring random blood glucose (RBG) levels using the Accu-Chek Performa glucometer with glucose test strips for blood glucose testing [8]. On an LCD screen, it displays the test result in five seconds. A woman was considered diabetic if her RBG level was > 140 mg/dL [8]. In this survey, women who voluntarily provided their blood sample for glucose testing were categorized as 'yes' if they were found to have diabetes, and 'no' if they did not. However, due to the unwillingness of some women to provide blood samples, a significant number of women were recorded as 'don't know'. Additionally, diabetes status was recorded as '0' to denote 'no' and '1' to denote 'yes'. Besides, diabetes was considered the dependent variable for the binary logistic model, while various socio-economic and bio-demographic factors were considered independent variables.

It is important to note that women who did not provide a blood sample and those who had never undergone blood testing for diabetes were recorded as 'don't know' and they were excluded from the study due to the lack of information on their diabetes status. This step was taken to ensure the reliability and validity of the study findings.

Data editing and statistical analysis

Descriptive statistics and a binary logistic regression model were carried out to examine the present status and relationships between SEFs, bio-demographic factors and diabetes. We consider non-respondents as missing values and cannot include them in our analysis since they have not responded to the survey. The total sample size was 7,24,115, where 65,105 samples are missing, so we have taken only 6,59,010 samples for this study. The authors constructed two separate models to determine the association between diabetes and other SEFs and bio-demographic variables. For the first model, religion, caste, place of residence, and wealth index were used as independent variable. For model two, seven variables were added—age group, education, marital status, parity, family size, BMI, and waist circumference- to determine how many variations resulted from adding these variables. The estimate was presented in the form of an adjusted odds ratio (AOR) with a 95% confidence interval (CI). To determine the goodness of fit of the two models, log-likelihood, deviance, and the likelihood ratio test (syntax: lrtest) values were reported. The percentage of diabetes prevalence in India was prepared using ArcMap 10.5 and then classified into five ranks: very high (above 3.25), high (3.25–2.33), medium (2.33–1.59), low (1.59–1.12), and very low (Below 1.12). The ArcMap 10.5 is a Geographical Information System (GIS) commonly used by researchers for creating, analyzing, and managing spatial data in a user-friendly environment. It was developed by the Environmental Systems Research Institute, Inc. (ESRI), California.

For a comparison prevalence of diabetes in India, a horizontal bar diagram was created using the Datawrapper online data visualization tool. In this diagram, it can be noted the relative change in diabetes among women of reproductive age (15–49 years). The time- frame of relative change was NFHS-4 (2015–2016) to NFHS-5 (2019–2021). The mathematical equation of relative change is as follows:

$$y = \frac{x_2 - x_1}{x_1} * 100$$

Where y = relative change, x_2 = final year, and x_1 = initial year

Here, we discussed the methods used to measure diabetes in NFHS-4 and NFHS-5. A finger-stick blood specimen was used to measure diabetes among women of reproductive-age (15–49 years) in NFHS-4. Both surveys (NFHS-4 and NFHS-5) used > 140 mg/dL as a cut-off for measuring diabetes among reproductive-age women in India. As per the NFHS, an additional medical evaluation was provided to women whose RBG test results exceeded 200 mg/dL. The FreeStyle Optium H glucometer with glucose test strips was used to measure diabetes in the NFHS-4 [21]. However, the Accu-Chek Performa glucometer with glucose test strips was used in NFHS-5 for the RBG test [8]. Due to the similar types of methods used in both surveys (NFHS-4 and NFHS-5), the results of this study were significant for drawing clear conclusions.

Results

Socio-economic and bio-demographic factors affecting diabetes in Indian women

Table 1 shows the effect of different socio-demographic factors on the prevalence of diabetes among the women in reproductive age group. According to the NFHS-5 survey, about 1.65% of women in India have diabetes. The results further showed that women above 35 years have a higher prevalence of diabetes (3.32%). In contrast, the lowest diabetes rate was observed among women between 15 to 24 years of age group (0.45%). The highest prevalence of diabetes was observed among divorced and widowed women (3.06%), compared to married (1.98%) and unmarried (0.45%), respectively. The highest percentage of diabetes was observed among the General Caste (2.12%), followed by the Scheduled Caste (1.68%), Other Backward Class (1.62%), and Scheduled Tribes (1.22%). Among the

Table 1 Effect of different socio-demographic factors on the prevalence of diabetes among the women in reproductive age group

Background Characteristics	Currently has Diabetes (%)	Sample Size
Age Group		
15–24	0.45	218,464
25–34	0.97	200,219
35 above	3.32	240,327
Marital Status		
Married	1.98	469,587
Unmarried	0.45	161,605
Others	3.06	27,818
Caste		
SC	1.68	133,951
ST	1.22	129,180
OBC	1.62	265,769
Others	2.12	130,110
Religion		
Hindu	1.55	511,844
Muslim	2.19	67,461
Christian	1.75	47,990
Others	2.00	31,715
Place of Residence		
Urban	2.39	159,814
Rural	1.41	499,196
Education		
No Education	1.85	154,282
Primary	2.12	77,551
Secondary	1.54	335,154
Higher	1.32	92,023
Wealth Index		
Poorest	0.96	135,573
Poorer	1.2	146,077
Middle	1.61	139,546
Richer	2.19	127,758
Richest	2.53	110,056
Parity		
0	0.59	207,046
1	1.60	89,584
2	2.25	169,210
> 2	2.30	193,170
Family Size		
Less than Four (< 4)	2.56	112,828
Four to Seven (4—7)	1.54	449,115
Above Seven (7 +)	1.13	97,067
BMI		
Underweight	1.10	609,961
Normal	0.76	1,315
Overweight	1.23	648
Obese	1.95	47,086
Waist Circumference		
< 80 cm	1.00	395,883
> 80 cm	2.80	263,127
Total	10,885	659,010

different religious groups, the Muslim (2.19%) population had the highest percentage of diabetes, followed by Jains and Buddhists (2.0%), and Christians (1.75%). However, the lowest prevalence of diabetes was observed among the Hindus (1.55%).

This study shows that women living in urban areas have a higher risk of diabetes (2.39%) compared to those residing in rural areas (1.41%). The highest percentage of diabetes was observed among the women having primary level education (2.12%), followed by no education (1.85%), secondary education (1.54%), and higher education (1.32%), respectively. In addition, the highest percentage of diabetes was observed in the richest wealth category (2.53%), compared to other economic categories. It was noticed that women who had more than two parities (> 2 live births) had a higher percentage of diabetes (2.3%) than women having lower parity. Women who have less than four members in their households are at a higher risk of getting diabetes (2.56%) than those who have more than four members (1.13%), respectively. The largest percentage of diabetes was observed among obese women (1.95%), followed by overweight (1.23%), underweight women (1.10%), and normal (0.76%). Women with waist circumferences above 80 cm had the highest occurrence of diabetes (2.80%).

Prevalence of diabetes in Indian women

The prevalence of diabetes among women in India is shown in Fig. 1. The highest prevalence of diabetes was found in Goa (4.09%), while among the southern states/UTs, the highest prevalence of diabetic women was observed in Kerala (3.91%). Meanwhile, the lowest prevalence of diabetic women have been observed in Nagaland (0.81%). In central India, Chhattisgarh and Madhya Pradesh have diabetes prevalence below 1.00%. Among western Indian states, diabetes ranges from 1.12% to 2.33%, except for Goa (4.09%). In north India, Ladakh (3.86%) observed the highest prevalence of diabetic women among UT. In North India, different levels of diabetes have been observed in states and UTs such as Jammu and Kashmir (2.69%), Delhi (2.27%), Punjab (2.2%), Haryana (1.83%), Himachal Pradesh (1.51%), and Rajasthan (1.12%). Despite the high prevalence of diabetes observed in most of the north Indian states and UTs, the lowest prevalence of diabetic women have been found in Uttarakhand (0.97%). Among the eastern Indian states, only

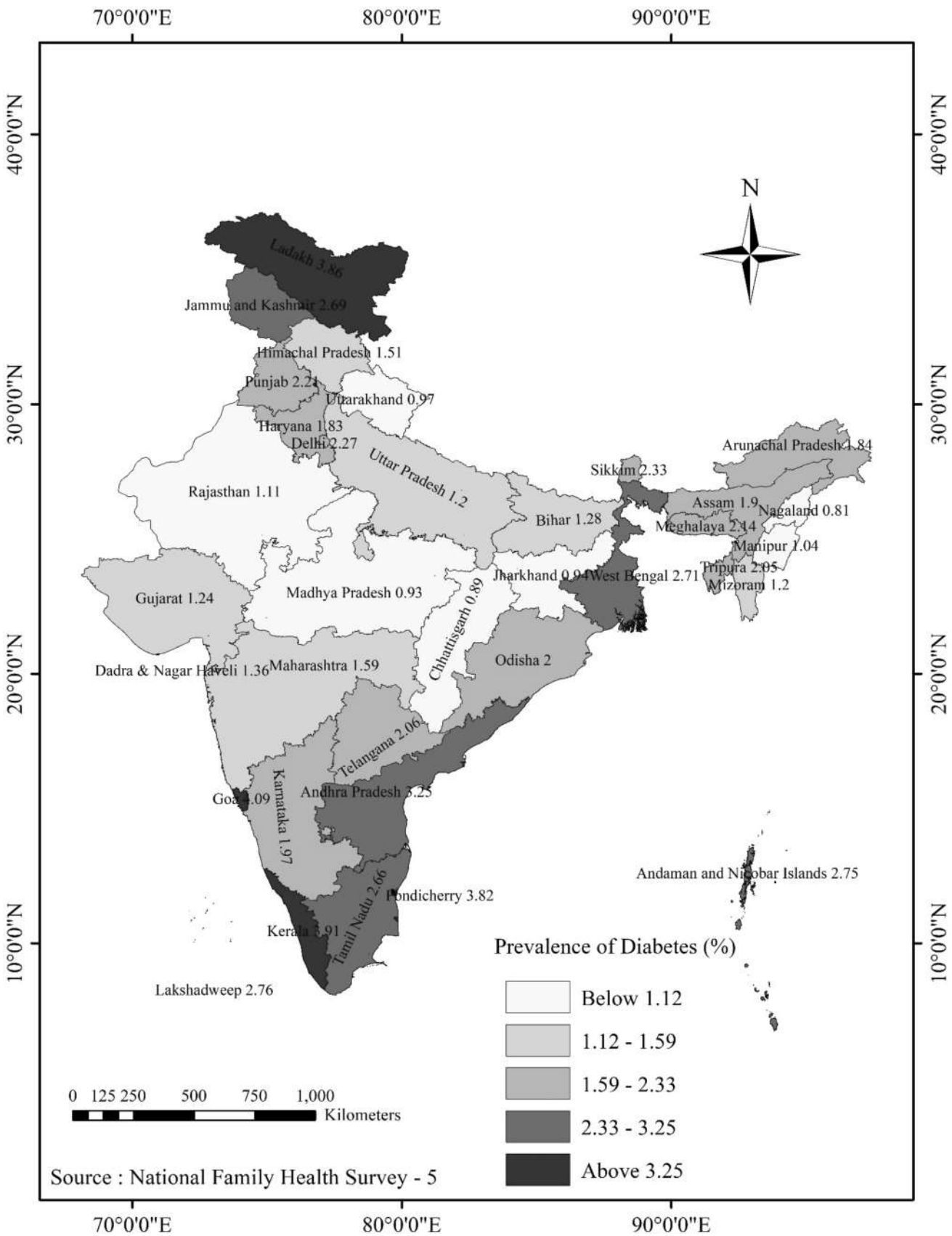

Fig. 1 Prevalence of diabetes among reproductive age women in India

Jharkhand had less than 1% of diabetic women, whereas the highest prevalence of diabetes was observed in West Bengal (2.71%), followed by Odisha (2%) and Bihar (1.28%). In northeast India, Meghalaya (2.14%) had the highest prevalence of diabetes, whereas Nagaland (0.81%) had the lowest prevalence of diabetes.

Diabetes trends in Indian women

The percentage of the relative change in diabetes among women in India is shown in Fig. 2. The highest percentage of the positive relative change in diabetes was observed in Assam (97.92%). In contrast, the lowest percentage of the positive relative change of diabetes was observed in Telangana (0.98%). The highest negative percentage change of diabetes was observed in Uttarakhand (-28.68%). And, the lowest negative percentage change of diabetes was observed in Himachal Pradesh (-1.95%). In India, the percentage of the relative change in diabetes was found to be considerably negative in 9 states and UTs. It also noted that the percentage of the relative change of diabetes in 9 states was between 0.0% to 25.0%. While in 8 states, the percentage of change in diabetes was between 26.0% to 50.0%.

Relationship between diabetes, socio-economic and bio-demographic factors in Indian women

The relationship between diabetic women and different socio-economic and bio-demographic factors is shown in Table 2. To establish a relationship, a binary logistic regression model was used. In this model, religion, place of residence, caste, wealth index, age group, education, marital status, parity, family size, BMI and waist circumference were considered the independent variables. And, diabetes was taken as the dependent variable. The results showed that Muslim women are 28% (AOR: 1.28, 95% CI: 1.21 to 1.35) more likely to have diabetes compared to Hindu women. Women residing in rural areas are 16% (AOR: 0.84, 0.80 to 0.87) less likely to have diabetes than women living in urban areas. The richest women are 84% (AOR: 1.84, 95% CI: 1.69 to 2.00) more likely to be diabetic than the poorest women. Women having primary and secondary education are 20% and 14% more likely to be diabetic than illiterate women. A positive relationship was observed in the chance of getting diabetes with increasing age, as 35–49 year-aged women showed 4.80 (AOR: 4.80, 95% CI: 4.37 to 5.27) times higher propensity of developing diabetes than 15–24-year aged women. Married and others women (divorcee and separated) are 41% (AOR: 1.41, 95% CI: 1.25 to 1.60) and 62% (AOR: 1.62, 95% CI: 1.41 to 1.87) more likely to be diabetic than unmarried women, respectively. A women with more than two parities have 22% (AOR: 1.22, 95% CI: 1.10 to 1.34) higher chances of being diabetic than women with no parity. Additionally, 4 to 7 and above 7 family members were found 31% (AOR: 0.69, 95% CI: 0.66 to 0.72) and 37% (AOR: 0.63, 95% CI: 0.59 to 0.68) less likely to be diabetic than women who belong to less than four family members, respectively. The BMI and diabetes probability was found to have positive relationship. Obese and overweight women have a 1.35 (AOR: 1.35, 95% CI: 1.18 to 1.47) and 1.06 (AOR: 1.06, 95% CI: 0.41 to 1.99) times higher chances of having diabetes than underweight women, respectively. Women who have a waist circumference over 80 cm are 1.69 (AOR: 1.69, 1.63–1.76) times more likely to develop diabetes.

Discussion

In India, the prevalence of diabetes among the women of reproductive age group has increased significantly over the last three decades, with some regional heterogeneity among the states and UTs [22, 23]. There is a significant relationship between disease burden, and socio-economic and demographic variables such as place of residence, wealth index, age-group, educational status, BMI, and waist circumference of reproductive age-group women [14, 24]. Additionally, diabetes is closely related to caste and religion [8]. Our results revealed that the prevalence of diabetes was higher among obese women (1.95%) and women over 35 years of age (3.32%). The study results reflected that the prevalence of diabetes was highly associated with the place of residence and economic status of women as those who were residing in urban areas with higher socioeconomic status had a higher percentage of diabetes [25].

Diabetes is affected by different socio-economic independent risk factors such as higher age (above 35 years), BMI (obese, and overweight), wealth index (Richest), and waist circumference (> 80 cm) of women in both rural and urban areas [26, 27]. However, the prevalence of diabetes was higher in the urban areas. This is mainly because of the higher socio-economic status of people, unhealthy dietary habits, lack of physical activities, consumption of salt or fat-rich foods, high blood glucose levels, and weight gain during childbearing age [17, 18]. Further, we observed that the prevalence of diabetes was declining with the increasing educational levels since highly educated women are more aware of their dietary habits, lifestyle, and family history [28]. A study by the Indian Council of Medical Research (ICMR) showed that the prevalence of diabetes was more prevalent among elderly women [29]. In our study, we observed a similar result as we found a significant association between the occurrence of diabetes and age-group. We also found that obese and overweight women are highly susceptible to diabetes than normal weight women, this is due to a lack of physical activity, and unhealthy dietary habits [30]. A past study found that women with > 80 cm waist

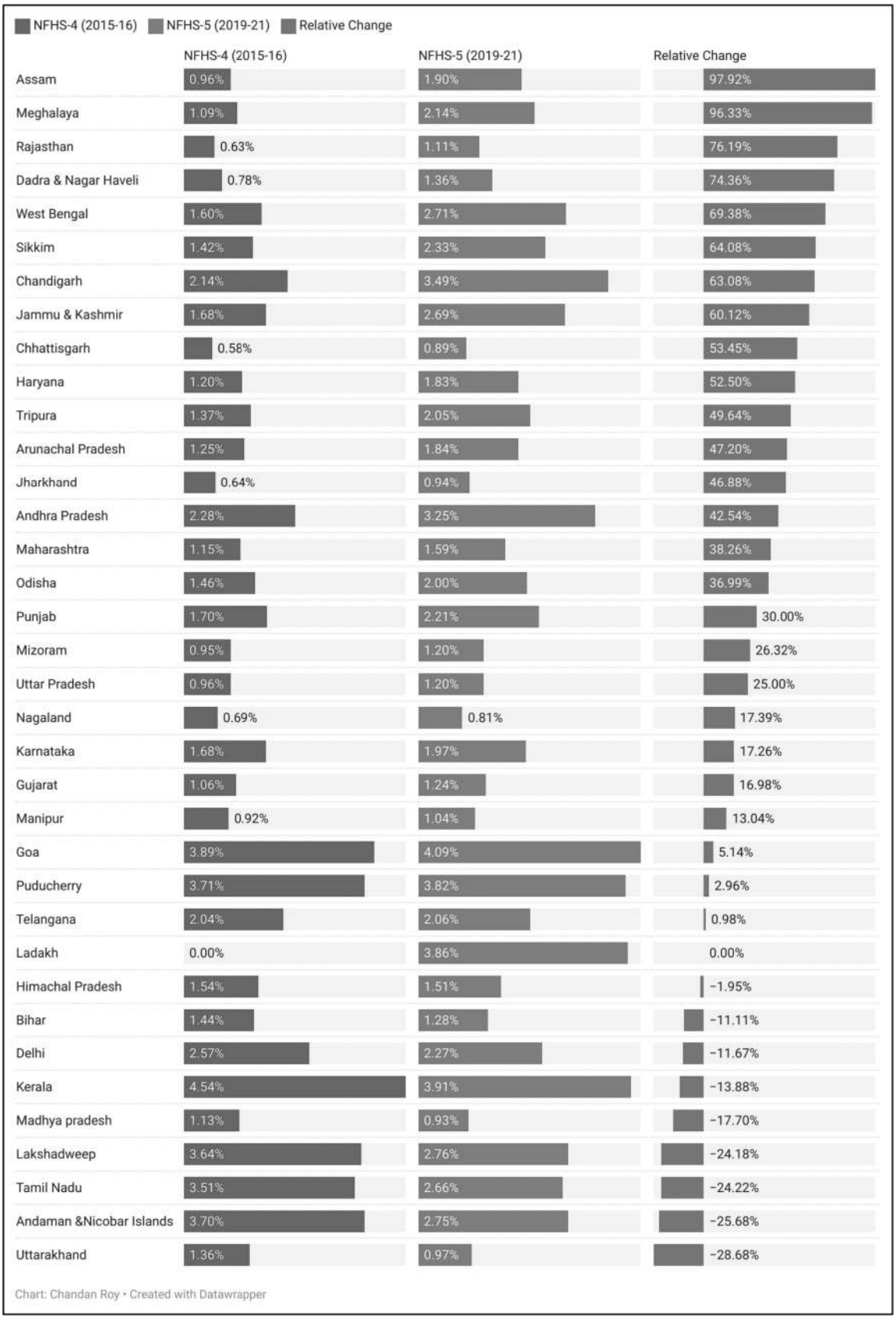

Fig. 2 Relative change of prevalence of diabetes among reproductive age women in India

Table 2 Establishing the relationship between diabetes and different socio-demographic factors among reproductive age-group women

Background Characteristics	Model 1 AOR (CI)	Model 2 AOR (CI)
Religion		
Hindu ®	1(1.00 to 1.00)	1 (1.00 to 1.00)
Muslim	**1.16 (1.10 to 1.23)*** **	**1.28 (1.21 to 1.35)*** **
Christian	**1.62 (1.47 to 1.79)*** **	**1.18 (1.06 to 1.30)** **
Others	0.89 (0.80 to 1.00)*	0.96 (0.85 to 1.07)
Place of Residence		
Urban ®	1 (1.00 to 1.00)	1 (1.00 to 1.00)
Rural	**0.76 (0.72 to 0.79)*** **	**0.84 (0.80 to 0.87)*** **
Caste		
SC®	1 (1.00 to 1.00)	1(1.00 to 1.00)
ST	**0.62 (0.57 to 0.68)*** **	**0.68 (0.62 to 0.74)*** **
OBC	**0.86 (0.82 to 0.90)*** **	**0.80 (0.76 to 0.84)*** **
Others	0.99 (0.94 to 1.05)	0.95 (0.89 to 1.00)*
Wealth Index		
Poorest ®	1 (1.00 to 1.00)	1(1.00 to 1.00)
Poorer	**1.17 (1.09 to 1.26)*** **	**1.12 (1.04 to 1.21)** **
Middle	**1.48 (1.38 to 1.59)*** **	**1.32 (1.22 to 1.42)*** **
Richer	**1.86 (1.74 to 1.99)*** **	**1.64 (1.52 to 1.77)*** **
Richest	**2.00 (1.85 to 2.15)*** **	**1.84 (1.69 to 2.00)*** **
Age Group		
15–24 ®		1(1.00 to 1.00)
25–34		**1.52 (1.38 to 1.67)*** **
35–49		**4.80 (4.37 to 5.27)*** **
Education		
No Education ®		1(1.00 to 1.00)
Primary		**1.20 (1.13 to 1.27)*** **
Secondary		**1.14 (1.08 to 1.20)*** **
Higher		0.88 (0.82 to 0.95)**
Marital Status		
Unmarried ®		1(1.00 to 1.00)
Married		**1.41 (1.25 to 1.60)*** **
others		**1.62 (1.41 to 1.87)*** **
Parity		
0 ®		1 (1.00 to 1.00)
1		1.03 (0.93 to 1.13)
2		1.10 (1.00 to 1.21)*
2+		**1.22 (1.10,1.34)*****
Family Size		
< 4®		1 (1.00 to 1.00)
4–7		**0.69 (0.66 to 0.72)*** **
7+		**0.63 (0.59 to 0.68)*** **
BMI		
Underweight®		1 (1.00 to 1.00)
Normal		0.56 (0.28 to 1.11)
Overweight		1.06 (0.41 to 1.99)
Obese		**1.35 (1.18 to 1.47)** **
Waist Circumference		
< 80 cm®		1 (1.00 to 1.00)
> 80 cm		**1.69 (1.63–1.76)*** **
_cons	**0.016 (0.015–0.017)*** **	**0.003 (0.011–0.007)*** **

Table 2 (continued)

Background Characteristics	Model 1 AOR (CI)	Model 2 AOR (CI)
Model Fit Statistics		
Log-likelihood	-64,406.94	-58,978.30
Deviance	1,28,813.88	1,17,956.60
Likelihood-ratio test[a]		**LR chi2(16) = 8149.03*** **

Experimental variable is diabetes among reproductive age-group women

AOR Adjusted Odds Ratio; *CI* Confidence Interval; ® represent reference category. The model I: Four socio-economic variables; Model II: Combined model with all study variables

* $p < 0.10$; ** $p < 0.05$; *** $p < 0.01$

[a]Assumption: Model I nested in Model II

circumference have a higher risk of metabolic complications due to high BMI which is similar to what we have found in our results [24].

A higher prevalence of diabetes was observed in states like Tamil Nadu, Kerala, Punjab, and Goa, with high epidemiological transition levels (ETL), followed by Delhi and Karnataka (higher middle ETL) [31] (Table 3). A study conducted by Atre (2019) shows that diabetes prevalence was higher in economically and epidemiologically advanced states (Kerala and Tamil Nadu) because these states are in an advanced stage of demographic transition, and have a higher burden of the elderly population [32]. According to the Indian Council of Medical Research- India DIABetes study, diabetes prevalence is higher in mainland states (Andhra Pradesh and Tamil Nadu) compared to northeast states (Manipur and Mizoram) [26]. Our study is in line with these findings. In addition, diabetes prevalence was higher in southern states such as Tamil Nadu, Kerala, Andhra Pradesh, and Goa. These states, which are in their advanced stage of demographic transition, and are more urbanized, have a high elderly population [22, 32]. However, the eight socio-economically backward states have a lower prevalence of diabetes, because, they are in the early stages of demographic transition, and experiencing higher fertility, lower levels of education, poverty, and lack of health and wellbeing [33, 34]**.** Besides, lower mortality and higher prevalence of NCDs were observed in Kerala due to the advanced stage of ETL [35, 36]. Meanwhile, regional variations of diabetes across various states and UTs were also observed in India based on different SEFs and GDP.

Due to Western dietary habits, rapid lifestyle changes, high blood glucose levels, and unhealthy lifestyles (smoking and alcohol consumption), Jammu and Kashmir has a significant proportion of diabetic women. Although Ladakh has a central obesity group that has a higher hip circumference, a higher BMI, a higher blood pressure (BP) (systolic and diastolic), and a higher prevalence of hypertension [37, 38]. These factors are closely associated with diabetes among women in Ladakh. Further, we observed an increased incidence of type 2 diabetes among reproductive women living in urban areas (e.g. Assam) because of thier high socio-economic status, frequent use of alcohol, and sedentary life style [39]. Religious rituals like Ramadan is one of the important reason for the higher occurrence of diabetes among Muslim women than other women. It is a serious health concern for the states like Assam, Jammu and Kashmir, and Lakshadweep [40, 41]. The states like Nagaland and Manipur have a lower proportion of diabetic women, because, they are in the early stage of demographic transition with a lower proportion of the elderly population. Additionally, in urban areas, we found a higher prevalence of diabetes among people having high socio-economic status, obese and overweight, widowed, separated and divorced, and physically inactive lifestyle [42, 43]**.**

Multiparty obese and overweight women are more vulnerable to diabetes than no parity women [44]. There is a significant relationship between diabetes and the age of an individual. A higher age-group means higher chances of getting diabetes [8]. Across the world, diabetes is more prevalent among the elderly population, those aged 60 years and above, due to eating habits, and lack of physical activities. In addition, the prevalence of diabetes peaks around 55 years. An estimate revealed that the prevalence of type 2 diabetes will increase to 7079 individuals per 100,000 by 2030, with major public health concerns for low and middle-income countries in the World [6, 44, 45].

A woman with a RBG level > 140 mg/dL is considered to be diabetic according to NFHS-5. It differs from the standard established by the American Diabetes Association (ADA), which is > 200 mg/dL [46]. And the NFHS-5 has not measured fasting plasma glucose (FPG) to measure diabetes. Besides, despite being a common health issue of hyperglycemia among pregnant women in South Asia, the NFHS-5 has not provided a comprehensive picture of hyperglycemia occurrence and its impact on pregnancy. Despite this limitation, this study provides insightful results about the prevalence of diabetes among reproductive age Indian women and how it relates to various SEFs and demographic factors. Because

Table 3 Ranking of the prevalence of diabetes among the states and UTs

Prevalence of diabetes (%)	Rank	States/ UTs	Reasons
Above 3.25	Very High	Kerala, Goa, Ladakh, Chandigarh, and Pondicherry	Advanced stage of demographic transition, high urbanisation, and a higher proportion of the elderly population in Kerala and Goa
3.25–2.33	High	Tamil Nadu, Andhra Pradesh, Jammu and Kashmir, West Bengal, Lakshadweep, and Andaman and Nicobar Islands	A high female work participation rate in Andhra Pradesh and Tamil Nadu, a higher percentage of the urban population in Tamil Nadu, Andaman and Nicobar Islands, and Lakshadweep, higher prevalence of obesity or overweight in Andhra Pradesh, Andaman and Nicobar Island, and Tamil Nadu
2.33–1.59	Medium	Punjab, Haryana, Delhi, Sikkim, Arunachal Pradesh, Assam, Tripura, Odisha, Telangana, Karnataka, and Meghalaya	In middle of the demographic transition stage, moderate work participation rate, medium living standard
1.59–1.12	Low	Gujarat, Dadra and Nagar Haveli, Maharashtra, Himachal Pradesh, Uttar Pradesh, Bihar, and Mizoram	Early stage of demographic transition and factors like lifestyle, genetics and healthcare
Below 1.12	Very Low	Uttarakhand, Rajasthan, Madhya Pradesh, Chhattisgarh, Jharkhand, Nagaland, and Manipur	Early stage of the demographic transition, very high proportion of the rural population, a very low female literacy rate, and a very low living standard

the NFHS-5 is a nationally-representative study covering the population as a whole, so, there is a little chance of underestimating diabetes prevalence depending on the distribution of hyperglycemia in the sample.

This study suggests a spatially-optimized target-oriented policy framework instead of a comprehensive national policy to address diabetes problems in the country. And maintaining healthy blood glucose levels, frequent screening of childbearing age group women, and awareness about the health consequences of diabetes will help in preventing this silent epidemic. At last, the authors suggest that further research should be focused on elderly diabetic women in India.

Conclusion

Diabetes shortens our life day by day and also reduced our quality-adjusted life years over time. Our study sheds light on the significant burden of diabetes in India, which is considered a silent epidemic, with considerable heterogeneity among states and union territories. We have identified several important factors that are strongly associated with diabetes, including BMI, waist circumference, wealth index, place of residence, and parity (live births). Our findings reveal that the prevalence of diabetes is higher among obese women residing in urban areas with higher socioeconomic status, compared to rural women with low socioeconomic status.

Our research emphasizes the urgent need for a targeted policy approach, including frequent health check-ups for women of childbearing age, successful implementation of the target-oriented national diabetes program, promotion of healthy aging, and increased public health awareness, particularly about Type-2 diabetes. We also stress the importance of early screening for diabetes to facilitate early detection and preventive measures. However, the regular monitoring of glycated haemoglobin (HbA1c) among diabetic women could be a possible healthcare intervention for diabetes control.

Furthermore, our study underscores the need for further research to formulate suitable policies that account for the varying prevalence of diabetes among states and union territories. In particular, future studies should focus on diabetes among elderly women, as this is an important and unique aspect that warrants further attention.

In conclusion, our research provides valuable insights into the burden of diabetes in India and highlights the significant associations between diabetes and various demographic and socioeconomic factors. Our findings underscore the need for targeted policies, increased awareness, and early screening to combat this silent epidemic. Further research, particularly focusing on diabetes among elderly women, will contribute

to the development of effective strategies to prevent and manage diabetes in India.

Strengths and limitations

The main advantages of the manuscript are its depiction of the prevalence of diabetes in the reproductive age group women, and it also analysed associations between diabetes and various socioeconomic and demographic factors. On the other hand, It also highlighted how some states and UTs have a higher or lower prevalence of diabetes.

However, the study mainly focuses on women in the reproductive age range because data on diabetes in the other age groups are not readily available in the dataset.

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Authors Contribution CR, SB, and VPS contributed to the conceptualization and study design. CR and SB performed the statistical analysis. CR, and SB interpreted the results and discussed the findings. CR, SB, VPS, AB, and SK drafted and finalized the manuscript. All authors have read and approved the final manuscript.

Data availability This study is based on the secondary data source that is available in the public domain through the Demographic and Health Survey (DHS) website (https://dhsprogram.com/data/available-datasets.cfm). The relevant authorities have obtained the necessary ethical approval for this survey. As a result, no additional ethical approval is required for this study.

Declarations

Ethical approval The necessary ethical approval has been taken by the respective authorities for this cross-sectional survey (NFHS-5). Hence, there is no need to take additional ethical approval for this study.

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Conflict of interest We don't have any conflict of interest to disclose.

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ORIGINAL ARTICLE

The effect of dapagliflozin use on cardiovascular outcomes in type 2 diabetic patients hospitalized with COVID-19

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Abstract

Objective We aimed to evaluate the impact of dapagliflozin on reducing major adverse cardiovascular events (MACE) and all-cause mortality in patients with COVID-19 and to assess whether it was associated with clinical improvement.

Methods Between March 2020 and July 2022, 446 diabetic patients hospitalized with COVID-19 were included in the study and were divided into two groups in terms of dapagliflozin use: 120 patients in the dapagliflozin group and 326 patients in the other oral antidiabetic (non-dapagliflozin) group.

Results Six (5%) deaths occurred in the dapagliflozin group and 58 (17.8%) in the non-dapagliflozin group (p=0.001). Lower rates of ICU admission were observed in the dapagliflozin group (8 (6.7%) vs. 67 (20.6%) patients) ($p = 0.001$). MACE occurred in 23 patients (19.2%) in the dapagliflozin group and 70 (21.5%) in the non-dapagliflozin group ($p = 0.689$). Higher age ($p = 0.001$) and higher urea ($p = 0.019$) were associated with increased risk of mortality. Dapagliflozin users had 3.937-fold lower risk of mortality (OR, 0.254; 95% CI, 0.093–0.697; $p = 0.008$). Multivariable logistic regression revealed that advanced age, active smoking, presence of peripheral artery disease, lower left ventricular ejection fraction, and glucose level were independently associated with MACE.

Conclusion We demonstrated that dapagliflozin treatment may be related with a reduced risk of mortality and lower ICU admission rates in diabetic patients hospitalized with COVID-19. Despite the limitations of the study, dapagliflozin could benefit COVID-19 patients with cardiometabolic risk factors, but further studies that control for our limitations are necessary.

Keywords Dapagliflozin · SGLT2 inhibitors · COVID-19 · MACE · Cardiometabolic risk factors

Introduction

The World Health Organization declared the novel coronavirus disease (COVID-19) outbreak a global pandemic on 11 March 2020, and since then, more than 604 million confirmed individuals and approximately 6.5 million deaths have been reported in different regions globally [1]. As established, COVID-19 leads to clinical outcomes ranging from mild to severe, including multi-organ failure and mortality. It causes a significant socioeconomic and health burden, especially in the elderly population, and it has been reported that many of the patients who died from the COVID-19 presented with comorbidities such as hypertension, diabetes mellitus, and cardiovascular disease [2]. There is a great unmet requirement for additional management options to reduce the risk of disease progression and major clinical events.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, also called gliflozins or flozins, are the latest class of antihyperglycemic medication to receive FDA approval for type 2 diabetes mellitus. They affect glucose and sodium reabsorption in the proximal convoluted tubule of the kidney, leading to a reduction in blood glucose without stimulating insulin release [3]. SGLT2 inhibitors may also have benefits in both primary and secondary prevention of cardiovascular and renal events due to their effects on weight loss and lowering of systolic and diastolic blood pressure [4]. The clinical results of SGLT2 inhibitors in reducing hospitalizations for heart failure in diabetic patients, regardless of preexisting atherosclerotic cardiovascular disease or previous history of heart failure, have drawn considerable attention to these drugs [5]. Recent studies have shown that SGLT2

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inhibitors provide significant clinical benefit on all-cause and cardiovascular mortality, as well as major adverse cardiovascular events (MACE) in diabetic patients with a history of atherosclerotic cardiovascular disease [5, 6]. These effects might aid the prevention of multi-organ failure and improve clinical recovery in patients hospitalized with COVID-19. However, clinical data regarding the effectiveness of SGLT2 inhibitors in providing organ protection in patients infected with COVID-19 remains unclear.

The aim of this study was to evaluate the efficacy and safety of dapagliflozin (a widely approved SGLT2 inhibitor) with respect to its effects on MACE, all-cause death, and new or worsening cardiometabolic conditions, as well as clinical outcomes, in diabetic patients with COVID-19.

Methods

Study design

The study was designed as a single-center cohort and was conducted between March 2020 and July 2022 in the Department of Cardiology and the Coronary Intensive Care Unit of Haseki Training and Research Hospital, Istanbul, Turkey. A total of 446 diabetic patients hospitalized with COVID-19 were enrolled in the study. Dapagliflozin was analyzed because it is one of the two SGLT2 inhibitors available in Turkey [7], and the only one among these that has been shown to independently improve cardiac parameters at 10 mg/day dosage [8]. All research procedures were evaluated and accepted by the Research Ethics Committee of Haseki Training and Research Hospital (date: May 11, 2022, decision no: 84-2022) and were conducted in agreement with the ethical standards specified in the Declaration of Helsinki.

Diagnosis

The diagnosis of COVID-19 was made according to the World Health Organization guidelines and confirmed by positive real-time reverse transcription polymerase chain reaction test for severe acute respiratory coronavirus 2 (SARS-CoV-2) using specimens derived from nasopharyngeal swabs or sputum, prior to or during hospitalization [9]. Diabetes mellitus was defined on the basis of patient-reported history, medical records, fasting glucose levels ≥126 mg/dL, non-fasting random glucose levels ≥200 mg/dL, glycated hemoglobin values (HbA1c) >6.5%, or use of oral hypoglycemic medication or insulin.

Inclusion and exclusion criteria

Participants younger than 18 years of age, with a history of malignancy or diabetic ketoacidosis, pregnancy, severe kidney or liver disease, type 1 diabetes mellitus, other known infections, and those receiving hemodialysis or insulin therapy were excluded from the study. Additionally, patients meeting these criteria who were defined to have severe COVID-19 (need for mechanical ventilation or vasopressor support) were not included in the study because of increased diabetic ketoacidosis risk. Finally, patients were excluded from the study in the event of adverse events leading to drug discontinuation or the development of conditions included in the exclusion criteria. Eighty-six patients were excluded from the study according to the exclusion criteria.

Patient groups and data acquisition

The patients were divided into two groups according to the type of antidiabetic used: those using dapagliflozin and those using other oral antidiabetics (non-dapagliflozin). All patients were treated according to national and international standard care guidelines for COVID-19.

In our clinic, old age (>64), hypertension, diabetes mellitus, hyperlipidemia, and smoking are considered cardiovascular risk factors. In our routine practice, dapagliflozin is recommended for patients who have at least one of these risk factors in addition to a diagnosis of type 2 diabetes mellitus, or who have a previous diagnosis of cardiovascular disease (ischemic heart disease, ischemic cerebrovascular disease, or peripheral arterial disease). Within the scope of the recommendation, dapagliflozin is started as monotherapy or combination therapy after the side effects and benefits of the drug are explained to the patients and consent is obtained. If the patient does not give consent, treatment management is switched to different antidiabetic drug combinations.

Clinical and demographic characteristics including age, sex, ethnicity, smoking status, family history of diabetes mellitus, current medications for diabetes mellitus, the number of oral antidiabetics used by patients, other medications, left ventricular ejection fraction, transthoracic echocardiography findings, and comorbidities (hypertension, hyperlipidemia, chronic obstructive pulmonary disease, coronary artery disease, peripheral artery disease) were obtained from patient files. Clinical outcomes, including length of stay in intensive care unit and hospital, MACE, and new or worsening conditions, including acute coronary syndrome, ischemic cerebrovascular disease, pulmonary embolism, deep vein thrombosis, and acute cardiac decompensation, were collected from in-hospital records.

The MACE composite endpoint was defined as a combination of acute coronary syndrome (ACS), cardiac arrest, stroke, acute heart failure, and cardiovascular death. ACS encompassed both acute myocardial infarction and unstable angina [10]. Acute myocardial infarction is defined by the presence of elevated cardiac biomarkers, such as troponins, and at least one of the following: new ischemic

electrocardiogram changes, symptoms associated with angina, changes in the function of viable myocardium on imaging, and identification of coronary thrombus by invasive coronary angiography [10]. Unstable angina pectoris was diagnosed in the presence of the same clinical presentation as AMI, but without cardiac biomarker elevation. Stroke was defined as a symptomatic focal neurological deficit lasting longer than 24 h caused by vascular events. Acute heart failure was defined as the rapid development or onset of signs and symptoms consistent with cardiac decompensation or inadequate cardiac pump function, which required urgent medical attention and hospitalization.

Patients were followed for at least 120 days for clinical outcomes. Patients received oral dapagliflozin 10 mg once daily or other appropriate oral antidiabetic(s). During the hospitalization, daily monitoring was performed for vital signs, laboratory results, clinical findings, and, if necessary, radiological evaluation. If discharged, patients continued on oral antidiabetic medication and were contacted by telephone or hospital visits on day 15 or 30. These patients were questioned for serious clinical outcomes, concomitant medications, and change of medications. All events were extensively reviewed and reported by the investigators with strict measures to ensure data quality.

Blood samples were obtained from the antecubital vein after 12-h fasting, at the time of hospital admission, and were centrifuged at 3000 rpm for 20 min to separate the serum. Blood biochemistry parameters including glucose, hemoglobin A1c (HbA1c), urea, and creatinine were determined using a Cobas 6000 autoanalyzer (Roche, Germany). Glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation, taking into consideration serum creatinine levels, age, and sex. All blood samples were examined within less than 1 h after the sampling.

Statistical analysis

All analyses were performed on IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA), and a $p < 0.05$ threshold was set for two-tailed significance. Histograms and Q-Q plots were used to determine the distributions of continuous variables. Mean ± standard deviation was used to summarize variables with normal distribution, while median (1st–3rd quartiles) was used for those with non-normal distribution. Absolute frequency (n) and percentage values were utilized for categorical variables. Normally distributed continuous variables were analyzed with the independent sample t-test. Non-normally distributed continuous variables were analyzed with the Mann-Whitney U test. Categorical variables were analyzed with chi-square tests or the Fisher exact test. Logistic regression analyses were performed to determine significant factors independently associated with mortality and MACE. Variables were analyzed with univariate regression, and those with p-values lower than 0.05 in this initial analysis were included into the multivariable logistic regression model.

Results

Four hundred and forty-six diabetic patients infected by SARS-CoV-2 were included in the study. Baseline demographic, clinical, and biochemical characteristics are shown in Table 1. There were 120 patients in the dapagliflozin group and 326 patients in the other oral antidiabetic drug (non-dapagliflozin) group. Mean age was 64.32 ± 10.92 years, and 233 patients (52.2%) were female. No significant differences were found between the groups in terms of age, sex, race, smoking status, and other medications at baseline (all, $p > 0.05$).

In the dapagliflozin group, 87 patients (72.5%) had hypertension, 75 (62.5%) exhibited hyperlipidemia, 26 (21.7%) had COPD, 28 (23.3%) presented with coronary artery disease, and 10 (8.3%) had peripheral artery disease. There was a significant difference between the two groups in terms of hyperlipidemia frequency ($p = 0.004$). The majority of patients (>90%) in both groups had a left ventricular ejection fraction greater than 50%. Of the study group, 377 patients (84.5%) were using biguanide, 178 (39.9%) using DPP-4 inhibitor, 121 (27.1%) using sulfonylurea, 60 (13.5%) using pioglitazone, 43 (9.6%) using empagliflozin, and 14 (3.1%) using acarbose. Of the patients in the dapagliflozin group, 51.7% received three different oral antidiabetic drugs, 25% received four, 19.2% received two, and 4.2% received one. The majority of patients in the non-dapagliflozin group used one (47.2%) or two (35%) oral antidiabetic drugs. There was a difference between the two groups in terms of the number of oral antidiabetic drugs used ($p < 0.001$). No significant differences were found between groups in terms of baseline laboratory results, including serum levels of glucose, HbA1c, urea, and creatinine, as well as glomerular filtration rate (all, $p > 0.05$).

Clinical outcomes of participants are shown in Table 2. MACE occurred in 23 patients (19.2%) in the dapagliflozin group and 70 patients (21.5%) in the non-dapagliflozin group ($p = 0.689$). Among the 23 MACE patients in the dapagliflozin group, 16 were diagnosed with new cardiovascular outcomes (CVO) and 7 with ACS. During the 120-day follow-up period, 2 out of 16 CVO patients and 1 out of 7 ACS patients died. Eight patients (6.7%) were admitted to the intensive care unit in the dapagliflozin group, while 67 patients (20.6%) had intensive care unit admission in the non-dapagliflozin group ($p = 0.001$). There were 6 (5%) deaths in the dapagliflozin group and 58 (17.8%) in the non-dapagliflozin group ($p = 0.001$). No significant differences

Table 1 Demographic, clinical, and laboratory characteristics of patients at baseline

	Total ($n = 446$)	Dapagliflozin use		p-value
		Yes ($n = 120$)	No ($n = 326$)	
Age	64.32 ± 10.92	64.81 ± 10.30	64.14 ± 11.15	0.570
Sex				
Female	233 (52.2%)	58 (48.3%)	175 (53.7%)	0.316
Male	213 (47.8%)	62 (51.7%)	151 (46.3%)	
Race				
Domestic	433 (97.1%)	117 (97.5%)	316 (96.9%)	1.000
Immigrant	13 (2.9%)	3 (2.5%)	10 (3.1%)	
Smoking status				
Non-smoker	206 (51.5%)	54 (47.4%)	152 (53.1%)	0.637
Ex-smoker	58 (14.5%)	18 (15.8%)	40 (14.0%)	
Passive smoker	81 (20.3%)	23 (20.2%)	58 (20.3%)	
Active smoker	55 (13.8%)	19 (16.7%)	36 (12.6%)	
Comorbidities				
Hypertension	326 (73.1%)	87 (72.5%)	239 (73.3%)	0.864
Hyperlipidemia	229 (51.3%)	75 (62.5%)	154 (47.2%)	0.004
COPD	81 (18.2%)	26 (21.7%)	55 (16.9%)	0.244
Coronary artery disease	109 (24.4%)	28 (23.3%)	81 (24.8%)	0.742
Peripheral artery disease	24 (5.4%)	10 (8.3%)	14 (4.3%)	0.150
Left ventricular ejection fraction				
≥50%	400 (89.7%)	110 (91.7%)	290 (89.0%)	0.512
≥30%–<50%	37 (8.3%)	9 (7.5%)	28 (8.6%)	
<30%	9 (2.0%)	1 (0.8%)	8 (2.5%)	
Glucose-lowering medications				
Dapagliflozin	120 (26.9%)			
Biguanide	377 (84.5%)			
Sulfonylurea	121 (27.1%)			
DPP-4 inhibitors	178 (39.9%)			
Pioglitazone	60 (13.5%)			
Empagliflozin	43 (9.6%)			
Acarbose	14 (3.1%)			
Number of oral antidiabetics				
1	159 (35.7%)	5 (4.2%)	154 (47.2%)	<0.001
2	137 (30.7%)	23 (19.2%)	114 (35.0%)	
3	120 (26.9%)	62 (51.7%)	58 (17.8%)	
4	30 (6.7%)	30 (25.0%)	0 (0.0%)	
Other medications				
Antiplatelet drugs	214 (48.0%)	58 (48.3%)	156 (47.9%)	0.928
Anticoagulant drugs	38 (8.5%)	14 (11.7%)	24 (7.4%)	0.210
Beta blockers	164 (36.8%)	50 (41.7%)	114 (35.0%)	0.193
Digoxin	10 (2.2%)	3 (2.5%)	7 (2.1%)	0.733
Amiodarone	4 (0.9%)	0 (0.0%)	4 (1.2%)	0.578
ACE inhibitors	118 (26.5%)	33 (27.5%)	85 (26.1%)	0.762
Angiotensin receptor blockers	128 (28.7%)	35 (29.2%)	93 (28.5%)	0.895
Calcium channel blockers	142 (31.8%)	41 (34.2%)	101 (31.0%)	0.522
Alpha blockers	15 (3.4%)	6 (5.0%)	9 (2.8%)	0.246
Vasodilators	34 (7.6%)	10 (8.3%)	24 (7.4%)	0.887
Diuretics	71 (15.9%)	16 (13.3%)	55 (16.9%)	0.447
Lipid-lowering medications	185 (41.5%)	60 (50.0%)	125 (38.3%)	0.027
Bronchodilators	75 (16.8%)	24 (20.0%)	51 (15.6%)	0.343

Table 1 (continued)

	Total (n = 446)	Dapagliflozin use		p-value
		Yes (n = 120)	No (n = 326)	
Laboratory values				
Glucose	188 (144–262)	204 (152–261.5)	183 (141–262)	0.339
HbA1c	7.8 (6.7–9.4)	7.9 (7.1–9.7)	7.6 (6.6–9.4)	0.073
Urea	37.95 (28–52)	38.1 (30.35–49.55)	37.8 (27–54)	0.879
Creatinine	0.89 (0.72–1.20)	0.90 (0.71–1.15)	0.88 (0.72–1.22)	0.896
Glomerular filtration rate	80 (54–96)	81.5 (55–97)	79 (54–96)	0.744

ACE inhibitors, angiotensin converting enzyme inhibitors; *COPD*, chronic obstructive pulmonary disease; *DPP-4 inhibitors*, inhibitors of dipeptidyl peptidase-4. Data are given as mean ± standard deviation or median (1st quartile–3rd quartile) for continuous variables according to normality of distribution and as frequency

Table 2 Clinical outcomes of patients in terms of dapagliflozin use

	Total (n = 446)	Dapagliflozin use		p-value
		Yes (n = 120)	No (n = 326)	
Newly occurred diseases				
Acute coronary syndrome	29 (6.5%)	7 (5.8%)	22 (6.7%)	0.896
Ischemic cerebrovascular disease	50 (11.2%)	16 (13.3%)	34 (10.4%)	0.488
Pulmonary embolism	20 (4.5%)	6 (5.0%)	14 (4.3%)	0.951
Deep vein thrombosis	5 (1.1%)	0 (0.0%)	5 (1.5%)	0.330
Acute cardiac decompensation	48 (10.8%)	9 (7.5%)	39 (12.0%)	0.239
Stay in intensive care unit	75 (16.8%)	8 (6.7%)	67 (20.6%)	0.001
Length of stay in hospital	9 (6–13)	8 (6–12)	9 (6–13)	0.119
Major adverse cardiac events	93 (20.9%)	23 (19.2%)	70 (21.5%)	0.689
Mortality	64 (14.3%)	6 (5.0%)	58 (17.8%)	0.001

Data are given as mean ± standard deviation or median (1st quartile–3rd quartile) for continuous variables according to normality of distribution and as frequency

were found between groups in terms of length of stay in hospital and new disease onset (including acute coronary syndrome, ischemic cerebrovascular disease, pulmonary embolism, deep vein thrombosis, and acute cardiac decompensation) (all, $p > 0.05$).

Multivariable logistic regression analysis revealed that age, dapagliflozin use, and urea were independently associated with mortality (Table 3). High age (OR, 1.050; 95% CI, 1.020–1.080; $p = 0.001$) and high urea (OR, 1.011; 95% CI, 1.002–1.019; $p = 0.019$) were associated with increased risk of mortality. In addition, we found that dapagliflozin users had 3.937-fold lower risk of mortality (OR, 0.254; 95% CI, 0.093–0.697; $p = 0.008$).

Multivariable logistic regression analysis revealed that age, smoking status, peripheral artery disease, left ventricular ejection fraction, and glucose level were independently associated with MACE likelihood (Table 4). We found that high age (OR, 1.060; 95% CI, 1.028–1.092; $p < 0.001$) and high glucose (OR, 1.004; 95% CI, 1.001–1.007; $p = 0.011$) were associated with increased risk of MACE. Active smokers had 7.261-fold higher risk of MACE than non-smokers (OR, 7.261; 95% CI, 2.636–20.000; $p < 0.001$). Patients with peripheral artery disease had 2.975-fold higher risk of MACE than those without (OR, 2.975; 95% CI, 1.089–8.130; $p = 0.034$). Patients with low left ventricular ejection fraction (<50%) had 3.823-fold higher risk of MACE than those with >50% (OR, 3.823; 95% CI, 1.633–8.950; $p = 0.002$).

Discussion

This study aimed to assess the impact of dapagliflozin on reducing cardiovascular events and all-cause mortality and its influence on improving clinical recovery in diabetic patients hospitalized with COVID-19. We found lower rates of ICU admission and mortality in the dapagliflozin group. Although not statistically significant, lower rates of MACE development were observed in the group receiving dapagliflozin compared to non-recipients. We also demonstrated by multivariable logistic regression analysis that higher age and urea were independently associated with increased risk of mortality, while dapagliflozin use was highly associated with

Table 3 Significant factors independently associated with the mortality by logistic regression analysis

	Univariable		Multivariable	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	1.056 (1.028–1.085)	<0.001	1.050 (1.020–1.080)	0.001
Sex, male	1.729 (1.010–2.960)	0.046	1.743 (0.967–3.143)	0.065
Race, immigrant	2.763 (0.825–9.256)	0.099		
Smoking status[(1)]				
Ex-smoker	0.311 (0.039–2.460)	0.268		
Passive smoker	0.222 (0.028–1.745)	0.152		
Active smoker	2.585 (0.952–7.019)	0.062		
Comorbidities				
Hypertension	1.021 (0.561–1.858)	0.947		
Hyperlipidemia	0.939 (0.553–1.595)	0.816		
COPD	1.177 (0.607–2.284)	0.630		
Coronary artery disease	1.776 (1.006–3.136)	0.048	1.294 (0.697–2.405)	0.414
Peripheral artery disease	0.528 (0.121–2.301)	0.395		
Left ventricular ejection fraction, <50%	2.058 (0.985–4.298)	0.055		
Number of oral antidiabetics use	0.625 (0.457–0.853)	0.003	0.919 (0.622–1.357)	0.670
Dapagliflozin use	0.243 (0.102–0.580)	0.001	0.254 (0.093–0.697)	0.008
Laboratory values at baseline				
Glucose	1.002 (0.999–1.004)	0.262		
Urea	1.017 (1.009–1.025)	<0.001	1.011 (1.002–1.019)	0.019
Nagelkerke R^2	-		0.174	

COPD, chronic obstructive pulmonary disease; *OR*, odds ratio; *CI*, confidence interval. [(1)]Reference category: non-smoker

Table 4 Significant factors independently associated with the major adverse cardiac events by logistic regression analysis

	Univariable		Multivariable	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	1.049 (1.025–1.073)	<0.001	1.060 (1.028–1.092)	<0.001
Sex, male	2.842 (1.753–4.608)	<0.001	1.083 (0.497–2.360)	0.842
Race, immigrant	1.143 (0.308–4.241)	0.841		
Smoking status[(1)]				
Ex-smoker	3.433 (1.616–7.296)	0.001	2.789 (0.965–8.059)	0.058
Passive smoker	1.712 (0.790–3.710)	0.173	1.465 (0.623–3.450)	0.382
Active smoker	8.824 (4.342–17.933)	<0.001	7.261 (2.636–20.000)	<0.001
Comorbidities				
Hypertension	1.443 (0.836–2.491)	0.188		
Hyperlipidemia	0.909 (0.576–1.436)	0.683		
COPD	0.610 (0.315–1.181)	0.142		
Coronary artery disease	2.275 (1.392–3.720)	0.001	0.647 (0.304–1.376)	0.258
Peripheral artery disease	6.078 (2.604–14.187)	<0.001	2.975 (1.089–8.130)	0.034
Left ventricular ejection fraction, <50%	5.812 (3.077–10.980)	<0.001	3.823 (1.633–8.950)	0.002
Number of oral antidiabetics use	0.722 (0.559–0.933)	0.013	0.767 (0.550–1.067)	0.116
Dapagliflozin use	0.867 (0.513–1.467)	0.595		
Laboratory values at baseline				
Glucose	1.004 (1.002–1.007)	<0.001	1.004 (1.001–1.007)	0.011
Urea	1.012 (1.004–1.019)	0.002	0.995 (0.984–1.006)	0.384
Nagelkerke R^2	-		0.292	

COPD, chronic obstructive pulmonary disease; *OR*, odds ratio; *CI*, confidence interval. [(1)]Reference category: non-smoker

decreased risk of mortality. Advanced age, active smoking, presence of peripheral artery disease, lower ejection fraction, and glucose level were independently associated with MACE.

COVID-19 is a systemic disease characterized by excessive, destructive cytokine storm resulting in acute lung injury with an increased risk for respiratory failure, cardiovascular and kidney complications, and mortality [11]. Studies have identified many risk factors for COVID-19-related mortality, including older age, obesity, male sex, ethnicity, chronic heart disease, and decreased kidney function [12]. Consistently, we showed that advanced age and higher serum urea levels were associated with increased mortality in patients hospitalized with COVID-19. The presence of underlying cardiometabolic comorbidities such as diabetes mellitus, cardiovascular diseases, hypertension, heart failure, and chronic renal failure has also been shown to be associated with poor prognosis in patients infected with COVID-19 [13]. Dalan et al. demonstrated in a retrospective, observational study of 717 patients with COVID-19 that patients with diabetes or hypertension presented with more severe infections that caused greater oxygen need and also ICU admission. Treatment with angiotensin-converting enzyme inhibitors had a beneficial effect, whereas treatment with angiotensin receptor blockers or DPP-4i had detrimental effects for immune signatures [14]. However, in contrast, Pérez-Belmonte et al. showed in a Spanish cohort study of 2666 COVID-19 patients with type 2 diabetes that the at-home use of metformin, DPP-4i, insulin, metformin+DPP-4i, metformin+SGLT2i, or metformin+insulin had no effects on in-hospital complications, mortality, need for ICU care, and mechanical ventilation [15]. Although the factors causing altered risk of progression, related complications, and mortality remain unclear, obesity, insulin resistance, increased susceptibility to endothelial damage, robust inflammatory response, and tissue hypoxia, as well as impaired target organ function and metabolism, are the possible underlying mechanisms involved in this deterioration [16, 17].

SGLT2 inhibitors (commonly known members include dapagliflozin, canagliflozin, empagliflozin) are indicated for blood glucose control in type 2 diabetes mellitus via glucose and sodium reabsorption in the proximal tubule and have recently been reported to have unexpected favorable effects on cardiovascular and renal outcomes [18]. Wiviott et al. demonstrated in a study with 17160 diabetic patients who were at risk for atherosclerotic cardiovascular disease that dapagliflozin treatment yielded a lower rate of cardiovascular mortality or hospitalization [19]. However, MACE likelihood was similar to those receiving placebo. McMurray et al. reported in a phase III, placebo-controlled study involving 4744 patients with heart failure and reduced ejection fraction that the risk of worsening heart failure or mortality from cardiovascular causes was lower in dapagliflozin recipients compared to placebo, regardless of the presence or absence of diabetes mellitus [20].

Previous studies have shown that SGLT2 inhibitors positively affect multiple biological pathways, including inhibition of glycolysis and stimulation of lipolysis, reduction of oxidative stress, and inflammation, as well as improved myocardial and endothelial function and oxygen-carrying capacity [17, 18]. These mechanisms, which may explain the protective effects of SGLT2 inhibitors, largely overlap with those dysregulated in COVID-19. In this setting, Kosiborod et al. examined the effects of dapagliflozin 10 mg versus placebo in reducing COVID-19 progression, complications and mortality in a randomized, double-blind, multicenter, placebo-controlled, phase III trial of 1229 patients hospitalized with COVID-19 (DARE-19) [21]. They found that management with dapagliflozin did not lead to reduced risk of organ dysfunction or mortality, or an improvement in clinical recovery after 30 days of follow-up. They showed numerically lower but non-significant rates of mortality and organ dysfunction among patients treated with dapagliflozin; however, their results may have been affected by the short follow-up period. There has been a need to organize large-scale clinical trials examining the effects of dapagliflozin use on clinical outcomes with a longer follow-up period (90–120 days). For this purpose, we designed our study with 120 days of follow-up and assessed MACE and mortality during this period. We showed statistically significant lower ICU admission and mortality rates with dapagliflozin treatment. In addition, we observed an independent relationship between the use of dapagliflozin and decreased risk of mortality by multivariable logistic regression. This supports the hypothesis that dapagliflozin confers beneficial effects on hospitalization and mortality. Optimizing glycemic control with drugs that have positive cardiac effects, such as dapagliflozin, offers several advantages in the context of the COVID-19 pandemic, especially for severe cases that may experience multiple inflammatory, respiratory, and clinical outcomes. Dapagliflozin may have been involved in providing beneficial control of excessive inflammation and reactive oxygen species production in diabetic patients with COVID-19. Although we observed lower rates of MACE in the dapagliflozin group compared to the non-dapagliflozin group, this difference was non-significant. Our results were consistent with previous studies showing positive cardiovascular effects with dapagliflozin. This protective influence of dapagliflozin may be due to its various effects on different biological pathways, including reduced oxidative stress and inflammation, increased production of ketone bodies, greater insulin sensitivity, improved myocardial and endothelial function, increased diuresis, stimulation of lipogenesis, and enhanced oxygen delivery to tissues [16, 17, 22, 23]. All of these biological mechanisms may have contributed to these

cardio-nephro-metabolic protective effects, either synergistically or separately. Therefore, we suggest that dapagliflozin may prevent or reverse the pathophysiological cycle leading to organ dysfunction, thus providing unexpected protective effects in COVID-19 patients. This may prove beneficial, rather than harmful, for cardiovascular outcomes [16].

Limitations

The primary limitation of the study is that it was conducted in a single center with a moderate sample size. Since the design of the study was retrospective, we could not include anthropometric data, which may have caused bias in the results. Furthermore, while we consider our general conclusions to be valid, any interpretation must take into account potential pitfalls such as unmeasured or uncontrolled confounders common in such retrospective studies. For example, genetic factors and psychosocial status were not analyzed, and it is plausible that these factors are common in both non-adherent and reduced survival patients. Additionally, although empagliflozin does not have the same cardiac benefits as dapagliflozin at the administered dosage [8], it is evident that the small group of patients who received empagliflozin in the non-dapagliflozin group could have affected results. But it is evident that this effect would have reduced the observed impact of dapagliflozin, rather than causing the emergence of an effect that was not present. It is crucial to mention that, beyond these specific points, our analyses controlled for (via regression) numerous other demographic and clinical factors that might influence the association between dapagliflozin treatment and mortality. As with any retrospective cohort study, it is not possible to draw causal inferences between pre-existing treatment with antidiabetics and the consequences of COVID-19. In addition, only hospitalized COVID-19 patients who did not have severe disease were included in the study, so we were unable to evaluate outcomes in non-hospitalized cases and patients with greater disease severity. This led to the inability to generalize the results. Finally, since the study was performed in the context of the COVID-19 pandemic, which has greatly affected patients' quality of life due to social distancing, limited physical activity, and difficult access to healthcare systems, it is impossible to completely exclude unmeasured confounding factors.

Conclusion

In conclusion, we demonstrated that dapagliflozin treatment may be associated with a reduced risk of mortality and lower ICU admission rates in diabetic patients hospitalized with COVID-19. Despite the limitations mentioned above, and the fact that there could be unavoidable confounding factors, it appears that dapagliflozin could have supportive effects due to the inferred benefits on target organs, disease progression, and mortality. Therefore, it is possible that COVID-19 patients with cardiometabolic risk factors could benefit from dapagliflozin treatment, indicating the need for further studies examining these effects.

Acknowledgements We appreciate all the participants who participated in the study.

Data Availability The original contributions presented in the study are included in the article material; further inquiries can be directed to the corresponding author upon reasonable request.

Declarations

Ethical approval All research procedures were evaluated and accepted by the Research Ethics Committee of Haseki Training and Research Hospital (date: May 11, 2022, decision no: 84-2022) and were conducted in agreement with the ethical standards specified in the Declaration of Helsinki.

Conflict of interest The authors declare no competing interests.

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ORIGINAL ARTICLE

Empagliflozin combined with short-term intensive insulin therapy improves glycemic variability and 1,5-anhydroglucitol in patients with type 2 diabetes: a randomized clinical trial

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Abstract

Objective We aimed to compare glycemic variability (GV) parameters using both a flash glucose monitoring (FGM) system and cardiometabolic risk parameters in hospitalized patients with type 2 diabetes mellitus (T2DM) between cohorts receiving short-term intensive insulin infusion (STII) plus empagliflozin (EMPA) combination therapy vs. STII therapy alone.

Methods In a 2-week, open-label, randomized, parallel-group clinical trial, newly diagnosed patients with T2DM [fasting plasma glucose (FPG) > 11.1 mmol/L or hemoglobin A_{1c} (HbA_{1c}) > 9.0%] or patients with poor glycemic control (HbA_{1c} > 7.0%) on oral antidiabetic drugs (OAD) received either STII+EMPA therapy ($n = 30$) or STII therapy alone ($n = 30$). FGM was carried over 14 days, and the data were used to calculate time in range (TIR [3.9–10 mmol/L]) and compare GV parameters. 1,5-Anhydroglucitol (1,5-AG) and cardiometabolic indicators of oxidative stress, inflammation, and vascular endothelial function were also compared.

Results After treatment, the TIR percentage was significantly higher ($p < 0.05$), and the time below range (TBR; < 3.9 mmol/L) was significantly lower ($p < 0.05$) in the STII+EMPA group than that in the STII group. The various measured glycemic parameters were significantly lower, and the average daily dose of insulin was also significantly lower in patients with STII+EMPA treatment (all $p < 0.05$). Plasma 1,5-AG levels were significantly higher ($p < 0.05$) in the STII+EMPA group than that in the control group.

Conclusions Newly diagnosed patients with T2DM or with poor glycemic control on OAD attained greater benefit and lower GV from STII+EMPA treatment than that for STII treatment alone. The 1,5-AG marker is a good indicator of the effects of short-term glycemic control.

Keywords Type 2 diabetes mellitus · Glycemic control · Glycemic variability · Flash glucose monitoring · Empagliflozin · 1,5-Anhydroglucitol

Abbreviations

GV	Glycemic variability
FGM	Flash glucose monitoring
T2DM	Type 2 diabetes mellitus
STII	Short-term intensive insulin infusion
EMPA	Empagliflozin
FPG	Fasting plasma glucose
HbA_{1c}	Hemoglobin A_{1c}
OAD	Oral antidiabetic drugs
TIR	Time in range
1,5-AG	1,5-Anhydroglucitol
TBR	Time below range
SGLT2	Sodium-glucose cotransporter 2 inhibitor
BMI	Body mass index
MBG	Mean blood glucose
LAGE	Largest amplitude of glycemic excursions
SDBG	Standard deviation of blood glucose
MAGE	Mean amplitude of glucose excursions
CV	Coefficient of variation
MODD	Mean daily differences
GA	Glycated albumin
TC	Total cholesterol
TG	Triglycerides
HDL-C	High-density plasma glucose
LDL-C	Low-density lipoprotein cholesterol
Hs-CRP	Hypersensitive C-reactive protein
MDA	Malondialdehyde

Extended author information available on the last page of the article

TNF-α	Tumor necrosis factor-α
IL-6	Interleukin-6
8-OHdG	8-Hydroxydeoxyguanosine
8-iso-PGF2α	8-Isoprostaglandin F2α
vWF	von Willebrand Factor
VEGF	Vascular endothelial growth factor
ELISA	Enzyme-linked immunosorbent assay

Introduction

Recent evidence has demonstrated that the prevalence of adult diabetes in China is as high as 11.2%, with type 2 diabetes mellitus (T2DM) accounting for over 90% of cases [1]. Glycaemic variability (GV) not only damages the function of pancreatic β cells but also leads to dysfunction in the kidneys, blood vessels, heart, and other target organs compared to glycemic control (indicated by a hemoglobin A_{1C} [HbA_{1C}] level of < 7%) [2].

Oral antidiabetic drugs (OAD) such as metformin are inconsistent and inadequate for maintaining glycemic control. Clinically, for patients with T2DM who are newly diagnosed or whose blood glucose is still substandard after combination therapy with OAD, short-term intensive insulin infusion (STII) is usually adopted to rapidly control blood glucose, promote functional recovery of pancreatic β cells, and thus reduce hyperglycemic toxicity and improve insulin resistance [3]. Studies have shown that insulin combined with OAD treatment is superior to insulin monotherapy in terms of reducing HbA_{1C}, preventing weight gain, and reducing hypoglycemic episodes [4, 5]. However, no consensus on the optimal therapy (STII plus OAD versus STII therapy) has been reached.

Empagliflozin (EMPA), a sodium-glucose cotransporter 2 inhibitor (SGLT2), has been shown to exert hypoglycemic effects by specifically inhibiting SGLT2 expression in renal tubular epithelial cells, reducing renal glucose reabsorption, and promoting urinary glucose excretion, with clear evidence of cardio-renal benefit [6, 7]. 1,5-Anhydroglucitol (1,5-AG) is the 1-deoxy form of glucose that is associated with clinical cardiovascular diseases [8]. The flash glucose monitoring (FGM) system, which provides a sensor with a handheld applicator to record glucose level every 5 min over 14 days, simplifies the process of glucose measurement and provides more accurate parameters for GV [9].

We have previously shown that EMPA combined with STII was able to effectively control blood glucose levels and shorten the time it took for blood glucose to reach the target level, without increasing the risk of hypoglycemia and urinary infection [10]. In this study, we compared parameters of GV, TIR, and cardiometabolic risk indicators, including oxidative stress, inflammation, and endothelial function, in Chinese patients with newly diagnosed T2DM or poor OAD-mediated glycemic control over 14 days, comparing the two popular treatment approaches of STII plus EMPA combination therapy and STII therapy alone.

Materials and methods

Trial design and intervention

This single-center, open-label, randomized, parallel-group clinical trial of patients with T2DM was conducted from April 2019 to March 2021. Seventy patients who had been newly diagnosed with T2DM or had been treated with OADs but had achieved inadequate glycemic control were randomly assigned to one of two groups, after consenting to this trial.

According to computer-generated random orders, the patients were assigned 1:1 to the STII group or STII combined with empagliflozin (STII+EMPA) group for 14 days, and a flash glucose monitoring (FGM) system was worn by all patients to record relevant measurements. Patients in both groups were administered insulin aspart (Novo Nordisk, Copenhagen, Denmark) and insulin degludec (Novo Nordisk, Copenhagen, Denmark) using an insulin pen (Novo Nordisk, Copenhagen, Denmark). The STII+EMPA group was administered an additional 10 mg of empagliflozin (Jardiance, Boehringer Ingelheim Pharma GmbH & Co., Ingelheim, Germany) orally, once per day before breakfast.

This study conformed to the provisions of the Declaration of Helsinki (1975, revised in 2013). The protocol was approved by the ethics committee of The Second Hospital of Hebei Medical University (No.2019-R078). All study participants provided written informed consent.

Inclusion and exclusion criteria

The inclusion criteria were as follows: [1] patients who had been newly diagnosed with T2DM [fasting plasma glucose (FPG) > 11.1 mmol/L or HbA1c > 9.0%, or those with poor glycaemic control (HbA1c > 7.0%) on oral antidiabetic (OAD) drugs [11]; [2] aged 18–70 years; and [3] body mass index (BMI) of between 18.0 and 35.0 kg/m^2. All the included patients were insulin-naive.

The exclusion criteria were as follows: [1] patients with type 1 diabetes mellitus; [2] pregnant or breastfeeding females; and [3] patients with one of the following diseases: acute or chronic hepatitis, severe acute or severe chronic diabetic complications, infection, recent trauma or surgery, renal dysfunction, acute or chronic pancreatitis, or a history of malignancy.

Procedures

Every patient provided a full medical history and physical examination at enrollment. Patients were provided with an education program on diabetes self-management, including diet and exercise counseling. According to the ADA guideline, we defined 3.9–10 mmol/L as the time in range (TIR), ≤ 3.9 mmol/L as the hypoglycemic range (also called the time below range, TBR), and ≥ 10 mmol/L as the hyperglycemic range [12].

The initial insulin dosage was 0.4–0.5 U/kg/day, with 40% of the total units being basal insulin (insulin degludec) and another 60% being prandial insulin (insulin aspart), injected equally before meals (three per day). The insulin dosage was adjusted for each patient by a trained physician, according to their blood glucose level measured by the FGM system. The dosage of basal insulin was based on FPG: for an FPG level of ≥ 10 mmol/L, insulin degludec was increased by 6U; FPG level > 7.9–10.0 mmol/L, insulin degludec increased by 4U; FPG level ≥ 6.2–7.9 mmol/L, insulin degludec increased by 2U [13]. Adjustment of the prandial insulin was based on the difference between postprandial and preprandial blood glucose values: when the difference value was > 4 mmol/L, insulin aspart was increased by 2–4 U [13]. If a hypoglycemic episode was reported, the patient was managed by decreasing the insulin dosage. No other hypoglycemic drugs were allowed during the study intervention period.

Determination of sample size

The sample size calculations were performed using the PASS software version 15 (NCSS Corporation, Kaysville, UT, USA). First, we assumed a power of 0.80, an alpha level of 0.05, and a medium effect size ($d = 0.4$), which results in $N = 56$ to perform a two-sided t test for differences between matched pairs. Second, adding 10% attrition rate at inclusion and post-assessment, we calculated that $N = 62$ participants needed to be enrolled.

Continuous glucose monitoring

Each subject was required to wear a FreeStyle Libre Pro®, an FGM system (Abbot Diabetes Care, Chicago, IL, USA), which was inserted by a specialized nurse during day 0 between 8:00 and 9:00 AM, on the back of each patient's upper arm.

The FGM system took one blood glucose reading every 5 min throughout the day and maintained glucose data for up to 14 days. The intraday GV parameters measured were as follows. Mean blood glucose (MBG): it was calculated as the mean of the daily average blood glucose levels during hospitalization. Largest amplitude of glycemic excursions (LAGE): the difference between the maximum and the minimum blood glucose value during the blood glucose monitoring period, which was < 4.4mmol /L. Standard deviation of blood glucose (SDBG): standard deviation of all measured values during blood glucose monitoring, the normal reference value was < 1.4 mmol/L. Mean amplitude of glucose excursions (MAGE): after removing all blood glucose fluctuations whose amplitude did not exceed a certain threshold (generally 1 SDBG), the average blood glucose fluctuation amplitude was calculated according to the direction of the first effective fluctuation, and the reference value was < 3.9 mmol/L. Coefficient of variation (CV): it was the ratio of the standard deviation to the mean MBG. Mean daily differences (MODD): the absolute value obtained by subtracting the corresponding blood glucose measured value within 2 consecutive days was calculated, and then, the average value was calculated (the average values of days 2~3 and 3~4 of MODD were used in this study), whose reference value was < 0.83 mmol/L.

Clinical and laboratory measurements

The clinical and laboratory parameters of the subjects, including sex, age, HbA1c, waistline, systolic blood pressure, diastolic blood pressure, ratio of newly-diagnosed diabetic patients, BMI, fasting plasma glucose (FPG), glycated albumin (GA), total cholesterol (TC), triglycerides (TG), high-density plasma glucose (HDL-C), and low-density lipoprotein cholesterol (LDL-C), as described previously [10], showed no significant differences before and after treatment in the two groups. Duration, family history of T2DM, and diabetic complications were evaluated.

Fasting venous blood samples were obtained at baseline and after 14 days of therapy for laboratory assessments. Plasma and serum were centrifuged (1500 *g* for 15 min at 4 °C) within 30 min of collection and stored at − 80 °C. Measurements of cardiometabolic indicators, such as serum hypersensitive C-reactive protein (Hs-CRP; EIA-1138), malondialdehyde (MDA; A003-1), tumor necrosis factor-α (TNF-α; EIA-0085), interleukin-6 (IL-6, EIA-0115), 8-hydroxydeoxyguanosine (8-OHdG; EIA-0705), 8-isoprostaglandin F2α (8-iso-PGF2α; EIA-0716H), von Willebrand Factor (vWF; EIA-1381), and vascular endothelial growth factor (VEGF; EIA-0078) were quantified using enzyme-linked immunosorbent assay (ELISA) commercial kits (Elisa Biotech, Shanghai, China) at the laboratory of the Second Hospital of Hebei Medical University. Plasma 1,5-AG levels were measured using an automatic biochemical analyzer (iCARE-2000, Changsha Sinocare Inc., Changsha, China).

Outcomes

The primary endpoints of this study were the patients' TIR and GV parameters over 14 days. Secondary endpoints based

on plasma 1,5-AG and biochemical measurements included serum Hs-CRP, MDA, TNF-α, IL-6, 8-OHdG, 8-iso-PGF2α, vWF, and VEGF, before and after treatment.

Statistical analysis

Data are presented as mean ± standard deviation, median (Q1, Q3), or percentage, as appropriate. Paired Student's *t*-tests or Wilcoxon signed rank tests were performed to compare changes before and after the intervention within the groups. The GV parameters were analyzed using a Gplus continuous glucose analysis system (Shanghai iMedpower Tech. Ltd., Shanghai, China) according to a previous study [14]. In Table 3, the comparison within group between baseline and after was done using paired *t*-test, and the comparison of between groups was done using *t*-test for independent samples or Wilcoxon rank sum test. All statistical analyses were conducted using Statistical Product and Service Solutions version 24.0 (IBM, New York, United States). Statistical significance was set at $p < 0.05$.

Results

Characteristics of the study subjects

Of the 70 patients who underwent screening, 66 were randomly assigned at baseline to the STII+EMPA group ($n = 33$) or STII group ($n = 33$) (Fig. 1), and 60 patients completed the study. The demographic and baseline clinical characteristics of the two groups were not statistically different (Table 1).

Comparison of GV parameters

All 60 participants had complete sets of FGM data during the 14-day treatment period. The percentage of TIR, which demonstrates glycemic control, was significantly higher, and the percentage of the hyperglycemic range was significantly lower, in the STII+EMPA group (both $p < 0.05$). Combination therapy showed a lower trend of hypoglycemia, although there was no difference between the two groups ($p > 0.05$; Table 2).

After the 14-day hospitalization period, the glucose data for each day were downloaded and analyzed (Fig. 2). The glycemic parameters MBG, LAGE, and SDBG were significantly lower in the STII+EMPA group than in the STII group, indicating that GV significantly improved after combination therapy with EMPA (Fig. 2). No statistically significant differences were observed for MAGE, CV, or MODD. Plasma 1,5-AG levels significantly increased from baseline until the endpoint in both groups (both $p < 0.05$). Compared to the STII group, the STII+EMPA group showed a better advantage in 1,5-AG [25.46 (3.30, 32.68) vs. 22.35 (8.5, 23.00) μmol/L, $p = 0.023$].

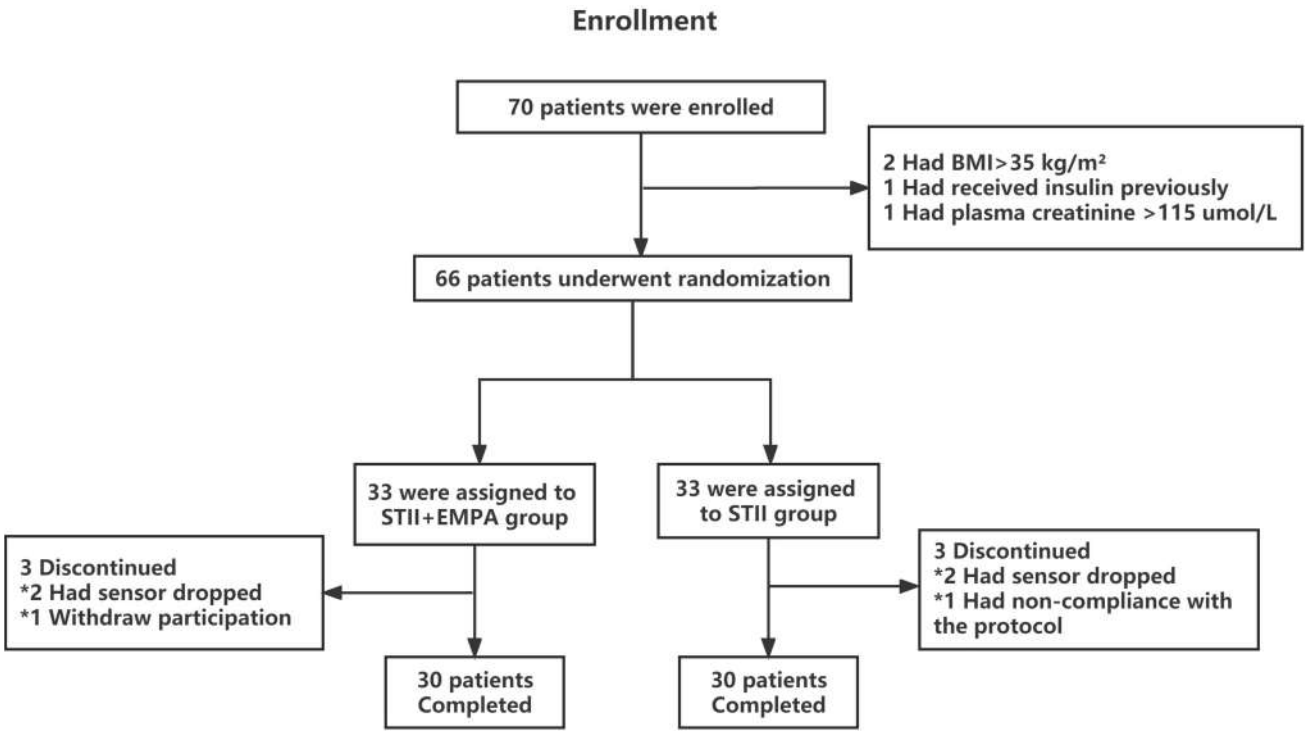

Fig. 1 Enrollment and outcomes of this study. STII: short-term intensive insulin; EMPA: empagliflozin

Table 1 Patients' characteristics at baseline

Items	STII + EMPA ($n = 30$)	STII ($n = 30$)	p
Gender (male/female)	21/9	19/11	0.584
BMI (kg/m^2)	26.66 ± 2.89	27.35 ± 3.36	0.406
Duration of diabetes (years)	4.07 ± 4.67	4.74 ± 4.48	0.582
Family history of T2DM (%)	46.67	40.00	0.602
Peripheral vascular disease (%)	70.00	76.67	0.559
Peripheral neuropathy (%)	76.67	73.33	0.766

Note: data are presented as means ± standard deviation or percentage. *BMI*, body mass index

Table 2 Flash glucose monitoring parameters of glycemic variability in patients during 14 days treated with STII+EMPA or STII alone

Items	STII+EMPA ($n = 30$)	STII ($n = 30$)	p
Mean percentage of time in target glucose range 3.9–10 mmol/L (%)	84.58 ± 9.42	79.25 ± 9.07	0.037
Mean percentage of time with hyperglycemia ≥ 10mmol/L (%)	12.73 ± 8.54	17.18 ± 9.14	0.031
Mean percentage of time with hypoglycemia < 3.9mmol/L (%)	2.69 ± 4.308	3.57 ± 4.86	0.436

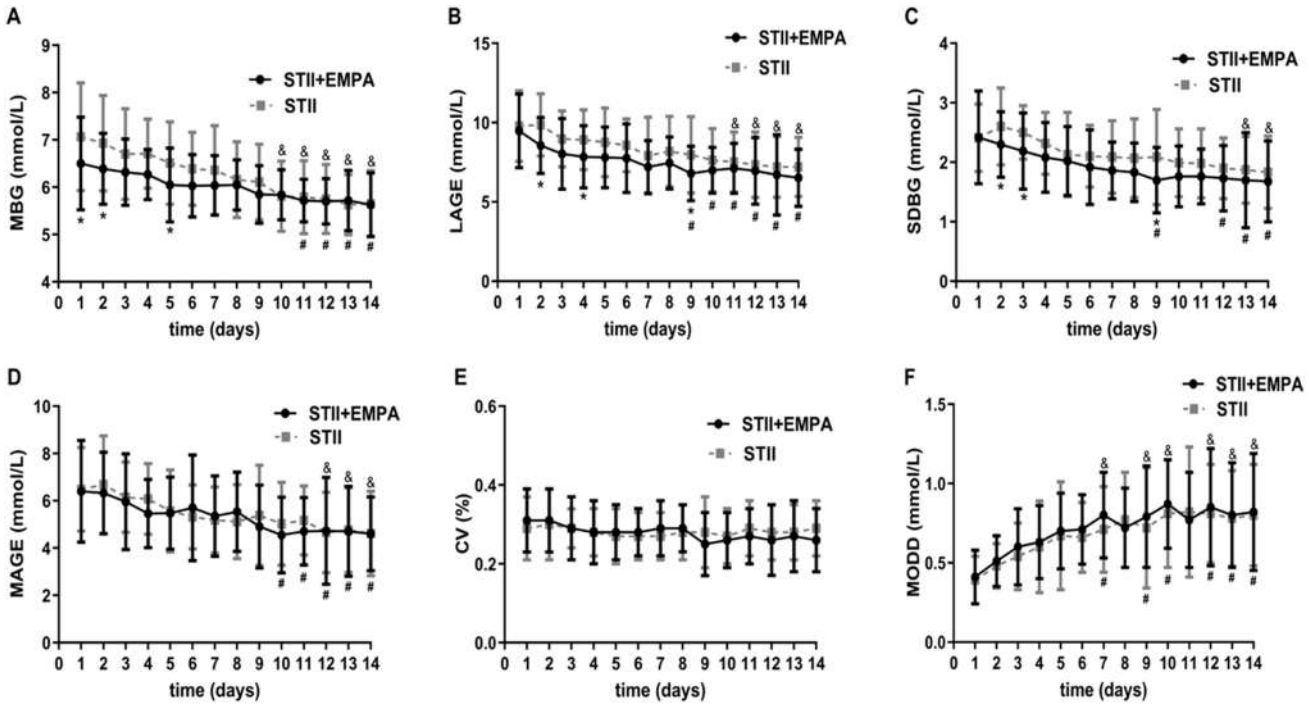

Fig. 2 MBG, LAGE, SDBG, MAGE, CV, and MODD values during a 14-day hospitalization period of the STII+EMPA and STII groups. MBG: mean blood glucose; LAGE: largest amplitude of glycaemic excursions; SDBG: standard deviation of blood glucose; MAGE: mean amplitude of glucose excursions; CV: coefficient of variation; MODD: mean daily differences. STII: short-term intensive insulin therapy; EMPA: empagliflozin. $^*p < 0.05$, comparison between STII+EMPA and STII groups; $^{\#}p < 0.05$, parameters from different time points compared with day 1 baseline data in the STII+EMPA group and $^{\&}p < 0.05$ in the STII group (Student's t-test)

Insulin dose administered between two groups

The average doses of prandial insulin administered were 17.74 ± 6.76 U vs. 21.37 ± 8.84 U in the STII+EMPA group and STII group, respectively ($p < 0.05$). The average dose of basal insulin was 12.29 ± 4.32 U for STII+EMPA therapy and 15.13 ± 5.83 U for STII therapy ($p < 0.05$). The average doses of insulin aspart and insulin degludec administered during the 14-day hospitalization period are shown in Fig. 3, which demonstrates that the dose of insulin used in

STII+EMPA treatment was significantly lower than the dose used in STII treatment.

Cardiometabolic risk parameters

Indicators of oxidative stress, inflammation, and endothelial function were comparable between the two groups at baseline (all $p > 0.05$). In the STII + EMPA group, significant changes from baseline to endpoint were found for serum MDA and vWF, but not in the STII group (both $p < 0.05$). Both IL-6 and 8-iso-PGF2α levels improved after treatment; however, there was no significant difference between the two groups. No difference was observed in the changes in serum Hs-CRP, TNF-α, 8-OHdG, and VEGF levels between the groups (Table 3).

Discussion

The results of this study indicated that hospitalized patients with T2DM who were newly diagnosed or responded poorly to OAD attained greater benefits from the addition of EMPA to STII therapy. Specifically, patients treated with this combination therapy achieved better glycemic control than those who were treated with STII therapy alone, as evidenced by improvements in TIR and 1,5-AG measured by the FGM system.

FGM systems have gradually become popular in clinical practice. The FGM system monitors glucose concentration in the interstitial fluid through subcutaneous implantation of a glucose sensor, indirectly reflecting the blood glucose level throughout the day, which helps clinicians intuitively monitor the GVs of patients and detect latent hyper/hypoglycemia [9].

Clinically, for patients with T2DM who are newly diagnosed or whose blood glucose levels are still substandard after treatment with OAD, STII therapy is usually considered to rapidly control blood glucose, promote functional recovery of pancreatic β cells, reduce hyperglycemic toxicity, and improve insulin resistance [3, 13]. The efficacy and safety of EMPA have been well established. In the EMPA-REG OUTCOME trial, EMPA, a sodium-glucose cotransporter 2 inhibitor, reduced the risk of major adverse cardiovascular events in patients with T2DM at high risk of cardiovascular events [7]. The latest clinical trials have shown that EMPA had beneficial effects on T2DM patients with chronic kidney disease and heart failure [15, 16].

Glycemic variability (GV), defined as a component of glucose homeostasis, is emerging as an important indicator to consider when assessing glycemic control in clinical practice. Compared to glycemic control, GV is more likely to activate oxidative stress, accelerate vascular endothelial cell damage, and promote the development of diabetic complications [17]. Although there is no consensus on GV, accumulating evidence has demonstrated that GV, including short-term and long-term GV, is associated with an increased risk of diabetic macrovascular and microvascular complications, mortality, and other adverse clinical outcomes [18].

To the best of our knowledge, there are currently no published clinical trials that have investigated the GVs of hospitalized patients with newly diagnosed T2DM or poor glycemic control when using OADs, who were treated by STII combined with EMPA therapy, evaluated by an FGM system. In the present study, TIR, TBR, MBG, LAGE, and SDBG were significantly improved when STII+EMPA therapy was used, compared to STII therapy alone, demonstrating that the combination was able to better narrow GV, which is similar to the finding of a previous study based on FGM [19]. Recent research has shown that TIR has a good

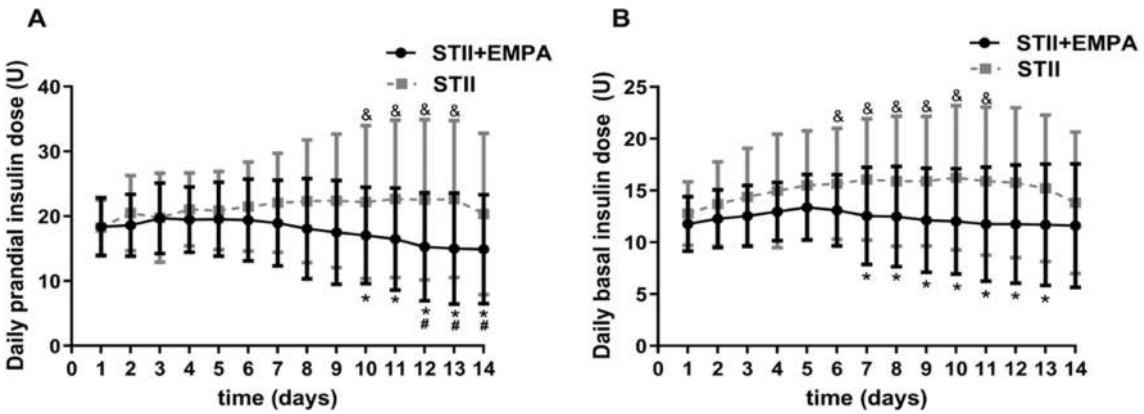

Fig. 3 Prandial insulin (**A**) and basal insulin (**B**) administered in STII+EMPA therapy and STII therapy alone. STII: short-term intensive insulin therapy; EMPA: empagliflozin. *$p < 0.05$, insulin dose compared between STII+EMPA and STII groups; #$p < 0.05$, insulin dose of different time points compared with day 1 baseline data in the STII+EMPA group and &$p < 0.05$ in the STII group (Student's *t*-test)

Table 3 Comparison of cardiometabolic risk factors between EMPA+STII group and STII group

Items		STII+EMPA	STII	*p*
1,5-AG (μmol/L)	Baseline	13.03 (3.00, 19.30)	13.88 (7.25, 18.35)	0.327
	After	38.49 (10.08, 45.68)	36.23 (22.28, 39.9)	**0.001**
	p-after/baseline	0.001	0.001	
	Change	25.46 (3.30, 32.68)	22.35 (8.5, 23.00)	**0.023**
Hs-CRP (mg/L)	Baseline	2.71 (1.05, 3.75)	3.28 ± 2.24	0.524
	After	4.48 (1.30, 4.48)	4.01 (1.05, 3.93)	0.994
	p-after/baseline	0.172	0.556	
	Change	− 1.71 (− 0.80, 0.95)	− 0.70 (− 0.65, 0.90)	0.561
MDA (nmol/mL)	Baseline	1.68 ± 0.49	2.12 (1.30, 2.15)	0.981
	After	2.37 (1.65, 2.45)	2.70 (1.50, 3.00)	0.852
	p-after/baseline	**0.001**	0.373	
	Change	− 0.70 (− 1.20, 0.10)	− 0.58 (− 1.35, 0.35)	0.861
TNF-α (pg/mL)	Baseline	29.01 ± 16.06	32.25 (20.50, 38.00)	0.680
	After	27.89 (18.45, 35.20)	41.60 (16.40, 38.80)	0.938
	p-after/baseline	0.647	0.156	
	Change	1.12 (− 6.60, 10.40)	− 9.35 (− 9.15, 6.95)	0.136
IL-6 (pg/mL)	Baseline	18.89 (12.80, 17.25)	18.90 (12.85, 17.80)	0.895
	After	13.55 (6.65, 12.35)	12.71 (6.10, 11.95)	0.963
	p-after/baseline	**0.001**	**0.001**	
	Change	5.34 (2.80, 9.20)	6.19 (2.90, 8.10)	0.408
8-OHdG (ng/mL)	Baseline	33.32 ± 15.43	39.04 (28.55, 43.00)	0.127
	After	41.14 (27.95, 46.20)	43.58 ± 20.97	0.641
	p-after/baseline	0.052	0.251	
	Change	− 7.81 (− 17.90, 1.80)	− 4.54 (− 19.65, 11.25)	0.551
8- iso-PGF2α (pg/mL)	Baseline	47.76 (19.10, 75.65)	50.65 (17.95, 77.80)	0.834
	After	27.64 (10.70, 27.70)	35.40 (9.00, 60.80)	0.907
	p-after/baseline	**0.001**	**0.001**	
	Change	20.12 (1.40, 47.85)	15.25 (− 0.25, 28.65)	0.431
vWF (U/L)	Baseline	32.96 (19.55, 42.45)	38.19 (26.10, 49.65)	0.197
	After	45.77 (27.50, 54.50)	43.47 (23.15, 59.30)	0.762
	p-after/baseline	**0.001**	0.264	
	Change	− 12.81 (− 24.70, 1.40)	− 5.27 (− 23.40, − 5.10)	0.215
VEGF (pg/mL)	Baseline	27.36 (17.85, 32.15)	40.95 (17.65, 37.55)	0.455
	After	24.60 (15.80, 28.90)	32.46 (14.05, 31.30)	0.975
	p-after/baseline	0.325	**0.045**	
	Change	2.76 (− 2.15, 6.90)	8.49 (− 2.05, 21.75)	0.106

Note: *STII*, short-term intensive insulin therapy; *1,5-AG*, 1,5-anhydroglucitol; *Hs-CRP*, hypersensitive C-reactive protein; *MDA*, malondialdehyde; *TNF-α*, tumor necrosis factor-α; *IL-6*, interleukin-6; *8-OHdG*, 8-hydroxydeoxyguanosine; *8-iso-PGF2α*, 8-iso prostaglandin F2α; *vWF*, von Willebrand Factor; *VEGF*, vascular endothelial growth factor. The comparison within group between baseline and after was done using paired *t*-test, and the comparison of between groups was done using *t*-test for independent samples or Wilcoxon rank sum test

correlation with diabetic microvascular complications and confirms its importance in clinical evaluation and therapeutic formulation [20].

In our previous study, the efficacy and safety of EMPA combined with STII therapy were confirmed in patients with T2DM. However, there were no statistically significant differences in HbA_{1c}, blood pressure, FPG, GA, abdominal circumference, BMI, TC, TG, CHOL, and LDL-C levels between the two groups at baseline and at the end of the study—suggesting that these indicators are not suitable for assessing short-term GV.

Studies have confirmed that 1,5-AG is inversely proportional to blood glucose levels within a 1–2-week window, which can reflect short-term GV, and its correlation with

GV is stronger than those of HbA_{1c} and GA [21]. A previous study explored the association between short-term GV and diabetes-related complications by evaluating 1,5-AG levels. The results showed that low levels of 1,5-AG were associated with an increased risk of retinopathy and incident chronic kidney disease [22]. Our study confirms the importance of evaluating 1,5-AG, showing that the reduction of 1,5-AG was greater in GV-improved patients who received STII+EMPA treatment than it was in patients who received STII treatment.

GV is more likely to induce oxidative stress, inflammation, and endothelial dysfunction, thus promoting the occurrence and development of diabetic macrovascular and microvascular complications [2]. MDA is a product of membrane lipid peroxidation and is an important indicator of oxidative stress. The isoprostaglandin metabolite iso8-iso-PGF2α possesses a stable structure and stable properties and is, therefore, considered an ideal biological index for evaluating oxidative stress injury in organisms [23]. Elevated levels of 8-OHdG, a biomarker of oxidative stress associated with DNA damage, contribute to early diagnosis and efficacy in monitoring patients with T2DM [24]. Hs-CRP is an acute reactive protein that is synthesized in the liver. TNF-α is a cytokine involved in systemic inflammation that causes acute reactions. Compared to other cytokines, IL-6 increases faster and earlier than hs-CRP and TNF-α in the inflammatory response. VEGF and vWF are credible biological markers of endothelial cell injury and dysfunction in the development of diabetes and its complications [25]. However, the results of this study showed that, after treatment, no significant difference was observed in any of these factors between STII+EMPA and STII treatment, suggesting not only that both treatments were beneficial for patients but also that these were not optimal biomarkers for evaluating short-term GV. Our findings were inconsistent with those of a previous study showing that 32 newly diagnosed patients with T2DM who were tested using a RayBiotech antibody array before and after 1 week of intensive insulin therapy with continuous subcutaneous insulin infusion showed decreased levels of many pro-inflammatory cytokines, including IL-6R and TNF-α, post-treatment [26]. Another study showed that after intensive insulin therapy for 1 week, patients with newly diagnosed T2DM were continuously treated with either rosiglitazone or insulin for 48 weeks, after which TNF-α, IL-6, hs-CRP, MDA, and 8-iso-PGF2α levels significantly improved in the rosiglitazone group [27]. There may be several reasons why our results differ from those of these studies. First, the intensive insulin therapy used differed between these studies. STII therapy (insulin aspart and insulin degludec) used during the 14-day hospitalization in our study is the optimal therapeutic regimen currently in clinical use, with the fewest side effects. Second, EMPA, a novel cardio-protective OAD, has been shown to attenuate myocardial oxidative stress in the hearts of diabetic mice, reduce inflammation, and exert a protective effect on the glomerular endothelia of diabetic mice [28, 29].

This study had some limitations as well: a small sample size; sex imbalance (with more male patients); patients were not followed up with to record post-discharge treatment regimens/results; and the influence of the FGM measurement error on blood glucose monitoring and practice was not considered. Further research with a larger sample size is warranted.

Conclusions

This study demonstrated that in hospitalized patients with newly diagnosed T2DM or poor glycemic control on OAD, the addition of EMPA to STII therapy could represent a preferred therapeutic approach that is more effective in improving GV and reducing insulin dose than STII therapy alone. The 1,5-AG marker is also suggested to be a better indicator than cardiometabolic risk parameters of the effects of short-term glycemic control.

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Author contribution ZH: research design, statistical analyses and interpretation of the data, drafting, and revision of the manuscript; LZ, YZ, YH, HZ, and MW: research design, statistics guidance, and revision of the manuscript; QZ, YG, and ZL: research design and conduction, collection of the data, and assistance in data analysis; YC, LJ, XZ, XW, JW, JZ, and HH: research conduction and collection of the data. All authors read and approved the final version of the manuscript.

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Data availability The original contributions presented in the study are included in the article material; further inquiries can be directed to the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate The protocol was approved by the ethics committee of The Second Hospital of Hebei Medical University (No.2019-R078). Informed consent was obtained from all individual participants included in the study.

Trial registration ChiCTR1900022412

Conflict of interest The authors declare no competing interests.

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ORIGINAL ARTICLE

Correlation between triglyceride-glucose index and related parameters and nonalcoholic fatty liver disease in northwest China

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Abstract

Objective The triglyceride glucose (TyG) index and obesity are significantly closely related to the incidence of nonalcoholic fatty liver disease (NAFLD). The study aimed to investigate the relationship among the TyG index and its related parameters [TyG-waist circumference (WC) and TyG-body mass index (BMI)] with NAFLD.

Methods This was a cross-sectional study involving 8401 subjects who underwent a health examination in Karamay, Xinjiang Province, China. TyG, TyG-WC, TyG-BMI were calculated with the established formula. NAFLD was diagnosed and classified by ultrasonography.

Results The prevalence of NAFLD was markedly increased with increasing levels of TyG, TyG-WC and TyG-BMI. Logistic regression analysis suggested that WC, BMI, TyG, TyG-WC and TyG-BMI were independent risk factors for NAFLD. In receiver operating characteristic (ROC) analysis, TyG-BMI showed the largest area under the ROC curve (AUC) for the detection of NAFLD (0.856, 95% confidence interval: 0.848 ~ 0.865), and the results of sex analysis were consistent. TyG-BMI values of 176.69 (sensitivity: 86.9%, specificity: 68.1%), 193.02 (sensitivity: 73.8%, specificity: 73.6%) and 167.73 (sensitivity: 86.3%, specificity: 74.4%) were the optimal cutoff points to predict NAFLD in all participants, males and females, respectively.

Conclusions This study demonstrated that TyG and its related parameters are significantly correlated with NAFLD. TyG-BMI is an effective predictor or clinical marker for identifying NAFLD.

Keywords Nonalcoholic fatty liver disease · TyG · TyG-BMI · TyG-WC

Introduction

With obesity becoming a serious public health problem, the incidence of nonalcoholic fatty liver disease (NAFLD) has increased year by year around the world, while the incidence of NAFLD in China has grown sharply in recent years. NAFLD has become the largest chronic liver disease in China and seriously endangers people's lives and health [1]. As a multisystem metabolic disorder, NAFLD is closely related to the incidence of obesity, type 2 diabetes mellitus, metabolic syndrome, cardiovascular disease and many other related chronic diseases [2–4]. Therefore, early identification and prompt intervention of NAFLD are particularly important.

The triglyceride glucose index (TyG), a product of fasting plasma glucose (FPG) and fasting triglyceride (TG), is an early biomarker of insulin resistance (IR). It has been recommended as a simple surrogate indicator for IR [5, 6]. Body weight health is strongly associated with IR and

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NAFLD, while waist circumference (WC) and body mass index (BMI) are two common measures of weight. For the past decade, an increasing number of studies have shown that TyG-related parameters, such as TyG-WC and TyG-BMI, are better than TyG alone in predicting IR [7]. IR plays an important role in the pathogenesis of NAFLD. The two not only exist together but also influence and promote each other [8, 9]. Recent studies have demonstrated that there is a significant correlation between TyG and its related parameters and the incidence of NAFLD [10–12]. Zhang et al. [13]conducted a cross-sectional study on 10761 people undergoing health examination in Wuhan, China, and found that TyG was effective in identifying individuals at risk for NAFLD. A TyG threshold of 8.5 was highly sensitive for detecting NAFLD subjects. However, the incidence of NAFLD is greatly affected by sex, diet, lifestyle and economic level, so there will be differences in the TyG threshold in different sexes and regions. Research of this difference has important clinical significance for the prevention and treatment of NAFLD.

This study aimed to further confirm the correlation between TyG and its related parameters and NAFLD by analyzing the data of physical examinees in Karamay, Xinjiang, China. For the first time, the optimal thresholds of WC, BMI, TyG and its related parameters for the early identification of NAFLD were evaluated in different sexes.

Methods

Study design

This study was a retrospective cross-sectional design. Adults who received health examinations at the Health Management Center of Xinjiang People's Hospital of Karamay from January 2018 to December 2018 were enrolled in the study. The subjects are mainly urban residents from Karamay, Xinjiang, who are concerned about their health and have annual physical examinations. Informed consent was obtained from the subjects during the medical examination.

The exclusion criteria included significant alcohol intake (> 140 g ethanol per week in men and > 70 g in women) [14]; hepatitis B and C; drug-induced liver disease (eg, corticosteroids, mipomersen, lomitapide, amiodarone, methotrexate, tamoxifen, valproate, and antiretroviral medicines); autoimmune liver disease; Wilson's disease, hemochromatosis and other metabolic liver disorders; missing data on age, sex, WC, BMI, FPG, TG or liver ultrasound. Finally, a total of 8401 participants were included in the study, consisting of 4721 men and 3680 women.

Clinical measurements

Sex, age, height, weight, blood pressure, WC, smoking history, alcohol consumption history and medical history were collected. Height and weight were accurately read to 0.1 cm and 0.1 kg, respectively. BMI was calculated as weight (in kilograms)/height square (in meters). WC was measured using plastic tape at the midpoint between the lowest rib and the superior border of the iliac crest as the subject exhaled normally. Venous blood samples were collected after 12 h overnight fast and analyzed for biochemical measurements, such as FPG, alanine aminotransferase (ALT), aspartate aminotransferase (AST), TG, and total cholesterol (TC). TyG = Ln [fasting TG (mg/dl) × FPG (mg/dl)/2] [15]. TyG-WC = TyG × WC [16]. TyG-BMI = TyG × BMI [17].

Diagnosis of NAFLD

Fatty liver was assessed by ultrasound scan (GE LOGIQ E9) by two experienced sonographers who were blinded to the clinical data. An increase in the echogenicity of the liver parenchyma appearing brighter than the cortex of the kidney, intrahepatic vessel blurring, and deep attenuation are the typical imaging features of fatty liver [14, 18]. NAFLD was diagnosed after the exclusion of diffuse fatty liver caused by alcohol, virus, autoimmunity, drugs, inherited metabolic diseases and other factors [14].

Statistical analysis

Data analysis was performed using IBM SPSS version 26.0 for Windows (SPSS Inc. Chicago, IL). Continuous variables are expressed as medians with interquartile ranges (IQRs) because of their skewed distribution, while categorical variables are presented as percentages. Differences between NAFLD and non-NAFLD individuals were analyzed using the Mann-Whitney U test.

Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using binary logistic regression analysis for NAFLD in WC, BMI, TyG, TyG-WC and TyG-BMI. Model 1 was unadjusted. Model 2 was adjusted for age, sex, smoking, ALT, AST, and TC.

Finally, receiver operating characteristic (ROC) curve analysis was performed to test the discriminative power of WC, BMI, TyG, TyG-WC and TyG-BMI for NAFLD. The sensitivity, specificity and Youden index were calculated, and the optimal cutoff point of variables for predicting NAFLD was derived from the point with the maximum Youden index. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

Characteristics of the participants

A total of 8401 participants were included in the present analysis, of whom 2162 were diagnosed with NAFLD by liver ultrasonic examination. The anthropometric indicators and biochemical data of the participants according to NAFLD category are presented in Table 1. Compared with non-NAFLD individuals, patients with NAFLD were older, with a higher proportion of males, and had higher BMI, WC, FPG, TG, TC, TyG and its related parameters, as well as higher liver enzyme levels, including ALT and AST (all $p < 0.001$).

Association between TyG, TyG-WC, TyG-BMI and NAFLD prevalence

The participants were divided into quartile groups according to TyG, TyG-WC, and TyG-BMI, and the prevalence of NAFLD in each group was calculated. As shown in Fig. 1, the prevalence of NAFLD was markedly increased along with the rising levels of TyG, TyG-WC, and TyG-BMI. The NAFLD prevalence of TyG, TyG-WC, and TyG-BMI in the highest quartile group was 54.5%, 61.3% and 60.1%, respectively, which was significantly higher than that in the lowest quartile group.

Logistic regression models evaluated the association of WC, BMI, TyG, TyG-WC, TyG-BMI with the risk of NAFLD

Logistic regression analysis showed that WC, BMI, TyG, TyG-WC, and TyG-BMI were all risk factors for NAFLD, before and after adjustments. The results are shown in Table 2.

Diagnostic accuracy of WC, BMI, TyG, TyG-WC, TyG-BMI for NAFLD

Figure 2 and Table 3 present the results of the ROC curve analyses of WC, BMI, TyG, TyG-WC, and TyG-BMI for predicting NAFLD. Among all included individuals, TyG-BMI showed the largest area under the ROC curve (AUC) for the detection of NAFLD (0.856, 95% CI 0.848 ~ 0.865), followed by TyG-WC (0.855, 95% CI 0.847 ~ 0.864). When analyzed by sex, TyG-BMI had the largest AUC for the detection of NAFLD in both males and females (0.807, 95% CI 0.794–0.819 and 0.883, 95% CI 0.868–0.897, respectively), suggesting that TyG-BMI is a good predictor for NAFLD in both male and female populations. In addition, the sensitivity of TyG-BMI in predicting NAFLD was significantly higher than other indicators in the whole population or female individuals, while it was slightly lower than TyG-WC in the male individuals. According to the maximum values of Youden's index, the optimal thresholds of TyG-BMI for predicting NAFLD in the whole population

Table 1 Characteristics of the participants for the presence of nonalcoholic fatty liver disease (NAFLD)

	ALL participants ($n = 8401$)	Non-NAFLD ($n = 6239$)	NAFLD ($n = 2162$)	p value
Age (years)	40 (15)	39 (16)	41 (15)	0.000
Men, n (%)	4721 (56.2)	2996 (48.0)	1725 (79.8)	0.000[#]
Women, n (%)	3680 (43.8)	3243 (52.0)	437 (20.2)	
Smoking, n (%)	2367 (28.2)	1443 (23.1)	924 (42.7)	-
Height (cm)	168 (12)	166 (13)	171 (10)	0.000
Weight (kg)	69.0 (20.0)	65.0 (17.0)	80.0 (17.0)	0.000
Waist circumference (WC)(cm)	85.0 (16.0)	82.0 (15.0)	95.0 (12.0)	0.000
Body mass index (BMI)(kg/m^2)	24.34 (5.14)	23.31 (4.40)	27.31 (4.52)	0.000
Fasting plasma glucose (FPG)(mmol/L)	5.34 (0.72)	5.26 (0.63)	5.62 (1.11)	0.000
Triglyceride (TG)(mmol/L)	1.30 (1.12)	1.12 (0.81)	2.11 (1.54)	0.000
Total cholesterol (TC)(mmol/L)	4.61 (1.17)	4.51 (1.11)	4.92 (1.18)	0.000
Alanine aminotransferase (ALT)(U/L)	20 (17)	17 (12)	32 (23)	0.000
Aspartate aminotransferase (AST)(U/L)	18 (7)	18 (6)	22 (10)	0.000
Triglyceride glucose index (TyG)	7.04 (0.90)	6.87 (0.74)	7.59 (0.83)	0.000
TyG-WC	602.22 (177.98)	563.37 (147.30)	722.46 (136.97)	0.000
TyG-BMI	172.73 (52.77)	161.18 (43.12)	208.99 (44.02)	0.000

Continuous data are presented as medians with interquartile ranges (IQRs), and categorical data are presented as numbers (%). Differences between NAFLD and non-NAFLD individuals were analyzed using the Mann-Whitney U test

[#] Proportion of men showing NAFLD vs. Proportion of women showing NAFLD

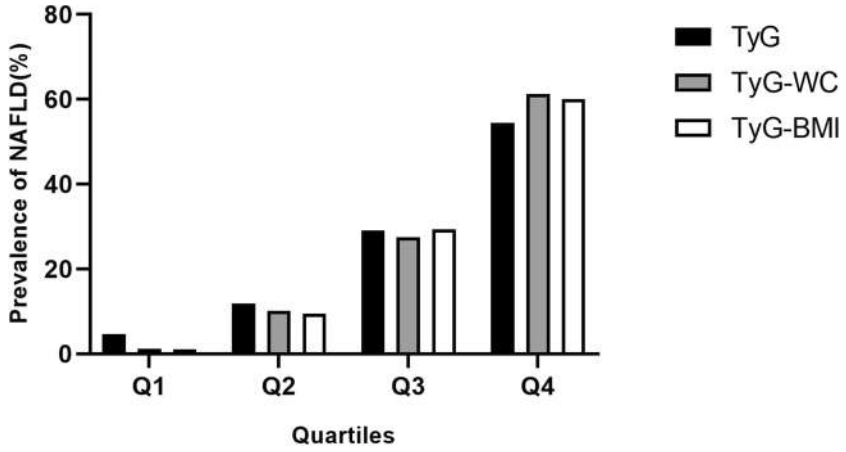

Fig. 1 Prevalence of NAFLD according to the quartiles of TyG and TyG-related parameters**.** Classification of TyG quartiles: Q1 (~6.63), Q2 (6.64~7.04), Q3 (7.05~7.53), Q4 (7.54~); TyG-WC quartiles: Q1 (~516.80), Q2 (516.81~602.22), Q3 (602.23~694.73), Q4 (694.74~); TyG-BMI quartiles: Q1 (~147.51), Q2 (147.52~172.73), Q3 (172.74~200.26), Q4 (200.27~). NAFLD, nonalcoholic fatty liver disease; WC, waist circumference; BMI, body mass index; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile

Table 2 The results of binary logistic regression analysis for the association of WC, BMI, TyG and TyG-related parameters with NAFLD risk

	Model 1 Crude OR(95%CI)	Model 2 OR(95%CI)
WC	1.127(1.120~1.134)	1.101(1.094~1.109)
BMI	1.397(1.373~1.422)	1.314(1.289~1.339)
TyG	6.424(5.821~7.090)	4.648(4.137~5.222)
TyG-WC	1.013(1.013~1.014)	1.013(1.012~1.013)
TyG-BMI	1.044(1.042~1.046)	1.038(1.035~1.040)

Model 1 was unadjusted

Model 2 was adjusted for age, sex, smoking, ALT, AST, and TC

WC, waist circumference; BMI, body mass index; TyG, triglyceride glucose index; NAFLD, nonalcoholic fatty liver disease

and in male and female individuals were 176.69, 193.02 and 167.73, respectively.

Discussion

In this study, we characterized a small cohort of subjects who underwent a health examination in northwestern China. Our present study showed that TyG and its related parameters are significantly correlated with NAFLD. Previous work demonstrated that the incidence of NAFLD is closely related to weight gain, central obesity, insulin resistance, atherogenic dyslipidemia and so on [14]. Therefore, the role of obesity indices and metabolic indicators (such as TyG) calculated from laboratory data in the early detection of NAFLD has been continuously explored in recent years [10–13]. This study demonstrated that WC, BMI, TyG, TyG-WC and TyG-BMI were independent risk factors for NAFLD, among which TyG-BMI was a better indicator. Among all subjects, the AUC value of TyG-BMI was up to 0.856, with a sensitivity of 86.9%, and the optimal threshold was 176.69.

IR in adipose tissue contributes to NAFLD through dysregulated lipolysis and inappropriate release of fatty acids, resulting in excessive delivery of fatty acids to the liver, which plays an important role in the occurrence and development of NAFLD [9]. On the other hand, previous studies have shown that overweight or obese individuals are at higher risk of NAFLD [19–21]. A meta-analysis suggested that obese individuals have a 3.5-fold increased risk of developing NAFLD, and there is an obvious dose-dependent relationship between BMI and NAFLD risk [22]. Another meta-analysis investigating the association between central and general obesity and the risk of NAFLD indicated that central obesity might pose a greater threat to national health than general obesity [23]. Recent studies reported that TyG and its related parameters (TyG-WC and TyG-BMI) obtained by TyG combined with the obesity indices WC and BMI were good indicators for IR prediction [5, 7, 15, 24]. Thus, the relationship between TyG and its related parameters and NAFLD has also attracted much attention. Zhang et al. [25] found that TyG-BMI was superior to TyG, BMI, TG and FPG in identifying NAFLD in a study of nonobese subjects over 20 years old in Wuhan Iron and Steel Company of China. The studies of Lim [26] and Khamseh et al. [12] indicated that compared with other relevant parameters, TyG-WC might be a better indicator for NAFLD prediction and had the largest AUC. In addition, Khamseh et al. [12] proposed that TyG-BMI was a better discriminator of liver fibrosis.

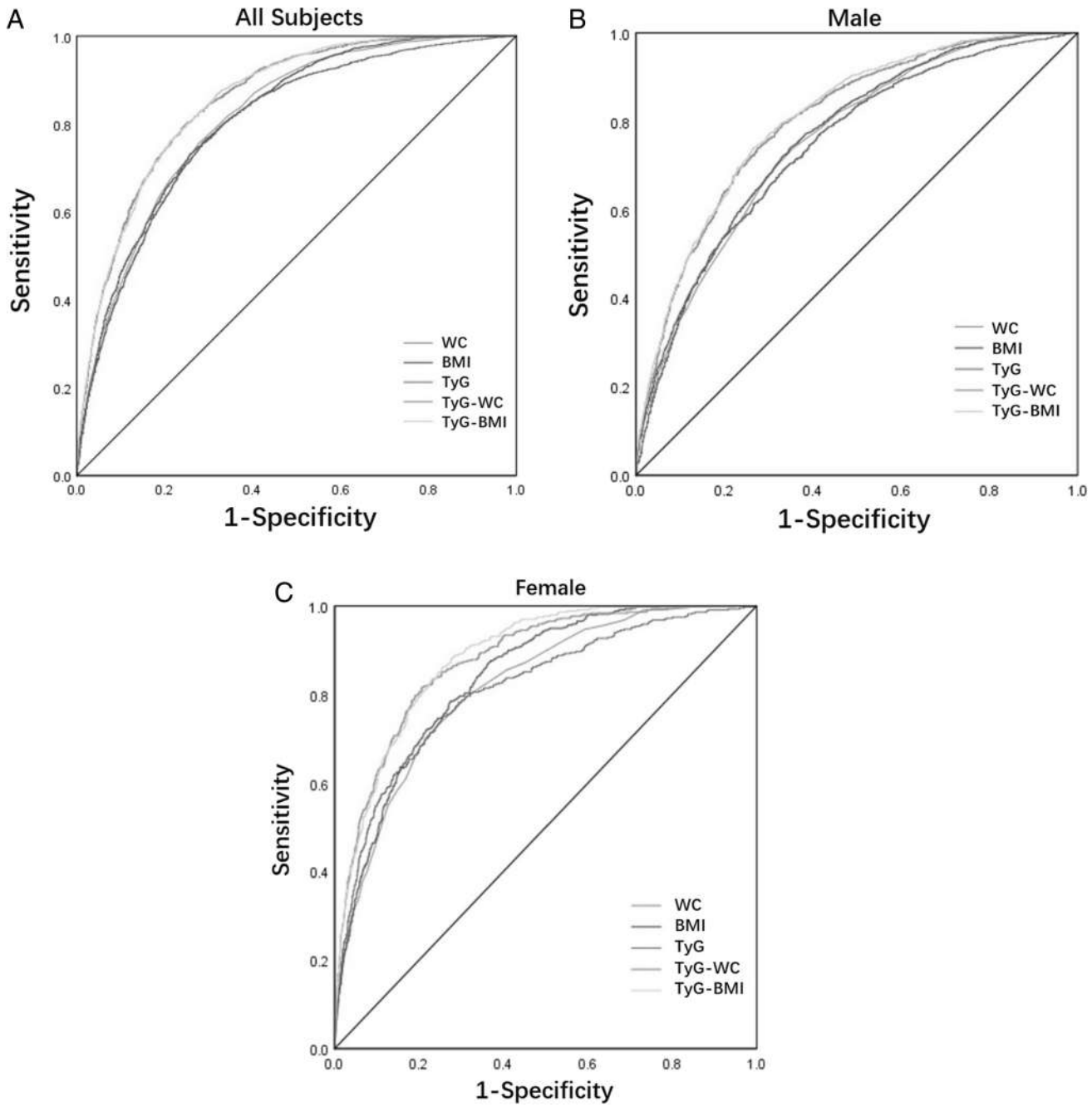

Fig. 2 The ROC curve of WC, BMI, TyG and TyG-related parameters for the prediction of NAFLD. **A** ROC curve for predicting NAFLD in all participants. **B** ROC curve for predicting NAFLD in men. **C** ROC curve for predicting NAFLD in women. ROC, receiver operating characteristic; WC, waist circumference; BMI, body mass index; TyG, triglyceride glucose index; NAFLD, nonalcoholic fatty liver disease

In this study, logistic regression analysis showed that WC, BMI, TyG, TyG-WC and TyG-BMI were independently associated with NAFLD. TyG-WC and TyG-BMI performed better than WC, BMI and TyG alone in NAFLD prediction, which was consistent with previous studies. The predictive value of these parameters for NAFLD in different sexes was analyzed for the first time. The results revealed that TyG-WC and TyG-BMI were still good indicators for predicting NAFLD in both men and women. TyG-BMI had the largest AUC value, which was slightly higher than TyG-WC. In different sexes, the optimal threshold of TyG-BMI was different; 193.02 in men was significantly higher than 167.73 in women, which is helpful for the identification of NAFLD in different sexes.

Table 3 The areas under the receiver operating characteristic curve, sensitivity, specificity and cutoff points for WC, BMI, TyG and TyG-related parameters for predicting NAFLD

Variables	Cut-off points	Sensitivity	Specificity	AUC	95%CI
All participants					
WC	88.50	0.756	0.722	0.816	0.806 ~ 0.825
BMI	25.21	0.754	0.714	0.809	0.800 ~ 0.819
TyG	7.24	0.733	0.740	0.804	0.794 ~ 0.815
TyG-WC	641.41	0.801	0.750	0.855	0.847 ~ 0.864
TyG-BMI	176.69	0.869	0.681	0.856	0.848 ~ 0.865
Men					
WC	90.50	0.740	0.644	0.755	0.741–0.769
BMI	25.41	0.739	0.651	0.762	0.748–0.776
TyG	7.38	0.693	0.665	0.743	0.729–0.757
TyG-WC	681.24	0.739	0.725	0.801	0.789–0.814
TyG-BMI	193.02	0.738	0.736	0.807	0.794–0.819
Women					
WC	83.50	0.707	0.780	0.818	0.798–0.838
BMI	24.23	0.785	0.725	0.837	0.819–0.854
TyG	6.97	0.751	0.743	0.813	0.790–0.835
TyG-WC	576.81	0.817	0.793	0.876	0.860–0.892
TyG-BMI	167.73	0.863	0.744	0.883	0.868–0.897

AUC, area under the curve; CI, confidence interval; WC, waist circumference; BMI, body mass index; TyG, triglyceride glucose index; NAFLD, nonalcoholic fatty liver disease

The prevalence of NAFLD varies due to differences in sex, race, region, lifestyle, economic level and diagnostic technique [27–29]. Consequently, the threshold of each metabolic indicator to predict NAFLD risk must be different. For example, Lim [26] found in a study of 7162 subjects who underwent physical examination in South Korea that the optimal cutoffs for NAFLD were 201.46 in TyG-BMI and 697.48 for TyG-WC, which were different from 176.69 and 641.41 in this study. However, Khamseh et al. [12] suggested that a TyG-WC value of 876 and TyG-BMI value of 259 were the optimal cutoff points to predict NAFLD and liver fibrosis, respectively, based on a study of a 30 to 65-year-old population in Iran. The TyG-WC value of 876 was significantly higher than the 641.41 in this study, which may be related to the difference in the included subjects. The BMI of the enrolled subjects in Khamseh's study was $\geq$25 kg/m2, while the median BMI of this study subjects was 24.34 kg/m2, the WC of the former was also significantly higher than that of this study subjects. In this study, the optimal metabolic indices and their thresholds for the identification of NAFLD were investigated in Xinjiang, China. The establishment of metabolic indices and thresholds in different regions needs to be confirmed by further research.

The present study indicates that patients with higher TyG values have more serious insulin resistance and NAFLD. This study is the first to explore the significance of TyG and its related parameters in the detection of NAFLD in Xinjiang and, for the first time, to analyze the optimal thresholds of each metabolic index in different sexes, which is more conducive to the identification of NAFLD.

We acknowledge the following limitations in this study. This study was a single-center, cross-sectional and retrospective study. The determination of the thresholds of these indicators requires further multicenter research. The number of subjects may have minimized the role of BMI on insulin sensitivity. Whether TyG-BMI can predict the occurrence of NAFLD in the future also requires more prospective studies. The diagnostic of NAFLD was ultrasonography, which has limited sensitivity. The results need to be confirmed with a larger study before being considered a routine clinical option.

Conclusion

In summary, our study demonstrated that the predictive value of TyG-related parameters comprising both TyG and obesity indicators (TyG-WC and TyG-BMI) for NAFLD is superior to TyG or obesity indicators alone. Hence, the calculation of TyG-WC and TyG-BMI in physical examination is very important for the prediction of NAFLD. It is worth noting that the thresholds vary by gender. Early lifestyle interventions are recommended in high-risk populations to reduce the incidence of NAFLD. Further study is needed, and a better understanding of the pathophysiological mechanism might provide insights into developing new strategies for treating NAFLD.

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Authors' contributions DL, HT and NL designed the study. DL drafted this manuscript. DL, SW, MZ, CX, HT and NL participated in the data collection and analysis. HT, NL and SW reviewed and revised this manuscript. All authors have read and agreed to the published version of the manuscript.

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Data availability The data for the current study used for statistical analysis are available from the corresponding author upon reasonable justification.

Declarations

Ethics approval and consent to participate The clinical study was approved by the Ethics Committee of Karamay People's Hospital, Xinjiang Second Medical College. The research protocol was implemented according to the principles expressed in the World Medical Association Declaration of Helsinki and under the International Ethical Guidelines

for Biomedical Research Involving Subjects (GIOMS, Geneva, 1993). Informed consent was obtained from all subjects.

Consent for publication Not applicable.

Competing interests The authors have no competing interests.

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ORIGINAL ARTICLE

Diagnosis of latent autoimmune diabetes after SARS–Cov2 vaccination in adult patients previously diagnosed with type 2 diabetes mellitus

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Abstract

Objective Acute worsening of glycemic control in diabetic patients and new–onset type I diabetes were reported after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines. Latent autoimmune diabetes in adults (LADA) is defined as a slowly evolving immune–mediated diabetes. A few cases of LADA diagnosed after SARS-CoV-2 vaccination have been reported in the literature. This study aims to report LADA after mRNA-based SARS-CoV-2 vaccinations in subjects with a history of well-controlled type 2 diabetes.

Methods We report four cases with LADA diagnosed after mRNA-based SARS-CoV-2 vaccine, BNT162b2 (Pfizer-BioNTech). In the medical history, all subjects had well-controlled type 2 diabetes with oral anti-diabetic medication. One case had autoimmune thyroid disease. One subject was presented with diabetic ketoacidosis.

Results Glycemic control of the presented cases had deteriorated 6–10 weeks after BNT162b2 vaccination. All patients were male and had high levels of glutamic acid decarboxylase 65 antibody (GAD65ab). An intensive insulin regimen was initiated at the time of diagnosis. The need for insulin therapy in two patients disappeared during follow-up. Two subjects were managed with basal insulin and oral antidiabetics. GAD65ab disappeared just 1 year after the diagnosis of LADA in a subject.

Conclusion In case of impaired glycemic control after SARS-CoV-2 vaccination in a well-controlled diabetic patient, LADA should be considered.

Keywords SARS-Cov-2 mRNA vaccination · Type 2 diabetes mellitus · Autoimmunity · Glutamate decarboxylase · Latent autoimmune diabetes in adults

Introduction

The coronavirus-19 (COVID-19) pandemic resulted in more than 6 million reported deaths [1], and diabetes mellitus is a risk factor for poor prognosis of COVID-19 [2–4]. The messenger RNA (mRNA) based severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines, the BNT162b2 (Pfizer-BioNTech) and the mRNA-1273 (Moderna), were developed rapidly and authorized for emergency use to prevent COVID-19. Due to the increased need for intensive care, mortality, and disease severity in diabetic patients [5–7], American Diabetes Association recommends prioritizing and offering severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines for diabetic patients [8].

The mRNA-based SARS-CoV-2 vaccines have been reported to trigger immune side effects in the endocrine system [9–12]. Moreover, acute deterioration of glycemic regulation following vaccination in diabetic subjects [13] and new-onset cases of type 1 diabetes after m–RNA–based SARS-CoV-2 vaccination have been reported in the literature [11, 14–21]. New-onset LADA after SARS-CoV-2 vaccine administration was recently reported in two subjects with preexisting pre/type 2 diabetes [22, 23]. However, data on the possible association between SARS-CoV-2 vaccination and the development or exacerbation of diabetes are quite limited [24, 25].

Herein, we report a case series of four patients with a history of well-controlled type 2 diabetes diagnosed as

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LADA after acute worsening of glycemic control following mRNA–based SARS-CoV-2 vaccine administration.

Materials and methods

Four cases followed at Ankara Güven Hospital were presented in this study. All patients had a history of well-controlled type 2 diabetes with oral anti-diabetic medication. Glutamic acid decarboxylase 65 antibody (GAD65ab) was tested with the enzyme-linked immunosorbent assay (ELISA) method (EUROIMMUN AG, Germany) (sensitivity 82% and specificity 99%, respectively; islet autoantibody standardization program, 2015).

Case presentations

Case 1

A 57-year-old male with preexisting type 2 diabetes mellitus for 5 years was admitted to the outpatient clinic with hyperglycemia. He did not have any symptoms. His medical history also included hypertension, metabolic syndrome, and autoimmune thyroiditis. He was receiving 1000 mg of metformin twice daily, 150 mcg of levothyroxine, and 80 mg of valsartan treatment. His blood glucose was well–controlled before SARS-CoV-2 vaccination. His previous blood tests were performed 3 months ago, and his HbA1c was 6.5%. He received the first BNT162b2 (Pfizer-BioNTech) in April 2021, and the second dose in May 2021. One month after the second dose of the vaccine, his blood glucose levels increased suddenly on self-monitoring without any changes in lifestyle and treatment. On physical examination, his body mass index (BMI) was 28.6 kg/m^2, and his waist circumference (WC) was 101 cm. At laboratory investigations, fasting blood glucose (FBG) was 257 mg/dL and glycated hemoglobin (HbA1c) was 8.5%. C peptide was 0.92 ng/mL (normal range 1.1–4.4 ng/mL), and GAD65Ab was > 2000 IU/mL (normal range: 0–10 IU/mL). An intensive insulin regimen with insulin aspart and glargine U300 was initiated. His insulin requirement constantly decreased during the follow-up, and insulin therapy was stopped because of hypoglycemia with low-dose insulin. Oral treatment with sitagliptin and metformin was resumed after insulin discontinuation. His diabetes was well-controlled at the first year visit.

Case 2

A 35-year-old male with preexisting type-2 diabetes mellitus for 3 years was admitted to the outpatient clinic with severe hyperglycemia. He had no personal or family history of autoimmune disease. His HbA1c level before vaccination was 6.2% with metformin treatment. The first and second doses of the BNT162b2 vaccine were administered in August and December 2022. Six weeks after the second dose, he had polyuria and polydipsia, and his blood glucose increased abruptly. On physical examination, his BMI was 36 kg/m^2, WC was 106 cm. FBG was 294 mg/dL, HbA1c was 8.0%, c-peptide level was 5.58 ng/mL, and GAD65Ab was 1408 IU/mL at laboratory investigations (Table 1). An intensive insulin regimen with insulin aspart and insulin glargine U100 was initiated. His need for insulin treatment decreased during the follow-up. Insulin was stopped, and treatment was switched to empagliflozin plus metformin 12.5/1000 at the 9th-month control.

Case 3

A 45-year-old male with a history of preexisting type-2 diabetes mellitus for 2 years was admitted to the outpatient clinic with uncontrolled diabetes. He had no personal or family history of autoimmune disease. He had been treated with empagliflozin/metformin 12.5/1000 mg and glimepiride 4 mg. His HbA1c level before vaccination was 6.5%. The first dose of the BNT162b2 vaccine was administered in August 2020. Forty days after the first dose of vaccine administration, he was admitted to the emergency unit and was diagnosed with diabetic ketoacidosis. On physical examination, his BMI was 25.1 kg/m^2, and his WC was 94 cm. At laboratory investigations, his FBG and HbA1C levels were high. He had ketosis, but not acidosis. His fasting insulin and c-peptide levels were at the lower limit of the normal range. GAD65Ab was 94 IU/mL (Table 1). He received intensive insulin treatment with insulin aspart and glargine U100. His insulin requirement decreased gradually. He has been treated with insulin degludec/insulin aspart 12 IU once daily and empagliflozin plus metformin 12.5/1000 mg BID for the last year.

Table 1 Clinical features and laboratory results of the subjects

	Case 1	Case 2	Case 3	Case 4
Age, years	57	35	45	38
Gender	Male	Male	Male	Male
Duration of preexisting diabetes	5	3	2	7
FPG (mg/dl)	257	294	352	350
HbA1c (%)	8.5	8.0	10.1	12.2
C-peptide (ng/mL)	0.92	5.58	0.97	0.7
GAD65Ab (IU/mL)	> 2000	1408	94	33
Time from vaccination to symptom onset (weeks)*	8	10	6	9

*After the first dose of the BNT162b2 vaccine

C-peptide normal range 1.1–4.4 ng/mL. *FPG* fasting plasma glucose (normal range: 70–100 mg/dL). *GAD65Ab* glutamate decarboxylase antibody-65 (normal range: 0–10 IU/mL). *HbA1c* glycated hemoglobin (normal range: 4.0–5.6%)

Case 4

A 38-year-old male with a history of type 2 diabetes mellitus for 7 years was admitted to our clinic. He had a history of acute coronary syndrome in February 2021. He did not have a personal or family history of autoimmunity. His BMI was 27 kg/m^2, and his WC was 102 cm. He was receiving vildagliptin, metformin, and empagliflozin treatment. His HbA1c level before vaccination was 7.5%. The first and second doses of the BNT162b2 vaccine were administered in April and May 2021. Five weeks after the second dose of the vaccine, he noticed an acute deterioration of self-monitored blood glucose measurements without lifestyle and treatment changes. His HbA1c level was 12.2%, and c-peptide was 0.7 ng/mL. GAD65Ab was 33 IU/mL and was positive at two separate laboratories (Table 1). Intensive insulin treatment was initiated. During the follow-up period, his need for insulin decreased. At the first-year control, c-peptide was 1.21 ng/ml. GAD65Ab returned a negative result, and the test was double-checked. Short-acting insulin was stopped. Insulin glargine U100 was continued with empagliflozin/metformin add-on therapy. His HbA1c and self-monitored blood glucose levels were at the target levels during follow-up.

Discussion

After administration of the mRNA-based SARS-Cov2 vaccine, new onset and exacerbation of several autoimmune diseases, including several type 1 diabetes cases [11, 14–21], have been reported [26–30]. Furthermore, two cases with newly diagnosed LADA possibly associated with SARS-CoV-2 vaccines have also been reported. In this study, we report LADA after mRNA-based SARS-CoV-2 vaccinations in four subjects with a history of well controlled type 2 diabetes.

Infection with SARS-CoV-2 was suggested to trigger or exacerbate type-1 and type-2 diabetes [31, 32]. Acute severe hyperglycemia and diabetic ketoacidosis have been reported in diabetic patients during and after COVID-19 infection [33–35]. Direct and indirect injury of pancreatic beta cells by SARS-CoV-2, molecular mimicry between SARS-CoV-2 proteins and human tissue, and autoimmune response triggered by adjuvants of a vaccine in genetically susceptible subjects have been proposed as potential mechanisms for SARS–CoV-2 vaccines induced hyperglycemia and autoimmunity [20, 24, 36].

Pancreatic beta cells express the angiotensin-I converting enzyme-2 (ACE–2) receptor, the functional host receptor for SARS-CoV-2. Direct damage to pancreatic beta cells via ACE-2 receptors and indirect damage caused by inflammatory cytokines were suggested as possible mechanisms for hyperglycemia after SARS-Cov2 infection/vaccination; however, could not have been proven in all studies [24, 37–39]. COVID-19–related acute-onset diabetic ketoacidosis was reported in patients with new-onset type-1 diabetes, and the need for insulin therapy decreased quickly [35]. Alleviated cytotoxic injury in β cells caused by COVID-19 infection was proposed as the mechanism for this rapid recovery [35].

Adjuvants of vaccines may trigger the autoimmune response in genetically susceptible subjects [40]. Type 1 diabetes was reported as a rare endocrine manifestation of autoimmune/inflammatory syndrome induced by adjuvants (ASIA) caused by vaccines against other viruses [41]. The mRNA-based SARS-CoV-2 vaccines do not contain adjuvants, but polyethylene glycol (PEG)–lipid conjugates may have an adjuvant role, and "mRNA" has self-adjuvant properties [42]. Moreover, molecular mimicry between mammalian proteomes and the spike protein of SARS-CoV-2 was demonstrated previously [36, 43]. Human SARS-CoV-2 spike protein had strong, and nucleoprotein had moderate reactivity with GAD65 antigen in the study of Vojdani et al. [36]. Onset or exacerbation of autoimmunity by COVID-19 infection and vaccines were suggested as a result of this cross-reaction [36].

Twelve cases of type 1 diabetes possibly related to SARS-CoV-2 vaccines have been reported [11, 14–21]. Most subjects were presented after mRNA-based vaccines, whereas one case was reported after inactivated whole virus vaccine [11, 14–21]. Besides, two cases with preexisting type 2 diabetes presented with acute deterioration of glycemic control and were diagnosed as LADA following m-RNA-based SARS-CoV-2 vaccination was reported in the literature [22, 23]. Follow-up data of these two reported cases with LADA was not available. Latent autoimmune diabetes in adults is an immune-mediated, slow-onset form of diabetes. It is known that LADA and type-1 diabetes have similar genetic susceptibility [44]. The main diagnostic criteria for LADA are the presence of islet autoantibodies, the absence of insulin requirement for at least 6 months, and presentation after 30 years of age [45]. The American Diabetes Association (ADA) defined LADA as T1DM, progressing more slowly than the classic disease [46]. However, World Health Organization (WHO) classified LADA as a hybrid form of diabetes with features overlapping with type 1 and type 2 diabetes (classification of diabetes mellitus. Geneva: World Health Organization; 2019. Licence: CC BY–NC–SA 3.0 IGO.). Patients with LADA do not require insulin treatment at diagnosis, as beta cells of pancreatic islets are functional at an early period [47]. Previously, it was demonstrated that GAD65ab is the most common islet autoantibody in LADA, and subjects with GAD65ab positivity had increased insulin requirements [48]. In our series, all patients had a diabetes duration of more than 2 years, indicating the slow progression of the disease. There was no case that we diagnosed

as LADA without history of type 2 diabetes. Three subjects experienced acute deterioration of glycemic control 4–8 weeks after the second dose of the BNT162b2 vaccine and one subject 40 days after the first dose. This finding was consistent with our previous report of new-onset type 1 diabetes cases after BNT162b2 vaccination [12]. In this case series, all subjects had GAD65ab positivity. None of our patients had a history of COVID infection.

Interestingly, GAD65ab disappeared in the first year of control of a subject, whereas three cases were still positive. Only one case had a history of autoimmune disease. All patients received an intensive insulin regimen after diagnosis of LADA. The need for insulin therapy decreased gradually in the whole group, and two cases stopped insulin due to hypoglycemia under low-dose treatment. Treatment strategy was determined according to blood glucose monitoring, repeated HbA1c, and c-peptide measurements at the follow–up [45]. Current evidence is insufficient to suggest a new onset of autoimmune diabetes caused by the BNT162b2 vaccine in our subjects with preexisting type-2 diabetes history. Also, it is not possible to exclude a coincidence. However, adjuvant-induced autoimmunity, molecular mimicry, or direct/indirect cytotoxic effects on pancreatic beta cells caused by the BNT162b2 vaccine may result in acute exacerbation of this slowly progressive disease. In our series, acute deterioration of glycemic control, followed by a rapid decline in insulin requirement, was consistent with the report by Kuchay et al. and our previous case series, which suggest an alleviation of autoimmune process or cytotoxicity short after exposure to SARS-CoV-2 or vaccine against SARS-CoV-2 [12, 35].

Conclusion

In conclusion, LADA should be considered in patients with pre-existing history of type-2 diabetes and experienced acute deterioration of glycemic control after SARS-CoV-2 vaccine administration. Pathophysiology of beta cell dysfunction and autoimmunity in SARS-CoV-2 and SARS-CoV-2 vaccine–related autoimmune diabetes should be investigated in further studies.

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Declarations

Statement of ethics The study was approved by Local Ethical Committee of Ankara Güven Hospital. Informed consent was obtained from all patients.

Conflict of interest The authors declare no competing interests.

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ORIGINAL ARTICLE

Association between dietary glycemic and insulin index/load and cardiometabolic risk factors among people with diabetes

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Abstract

Objective Limited studies have been conducted on insulin index/load, with inconsistent results regarding the glycemic index/load in relation to cardiometabolic risk factors among people with diabetes. The present study aimed to reveal the association of dietary glycemic index and load and dietary insulin index and load with cardiometabolic risk factors among people with diabetes.

Method This cross-sectional study was performed on 88 adults with diabetes who enrolled in the Cohort Study of Employees of Shiraz University of Medical Sciences. The scores of dietary glycemic index (DGI), dietary glycemic load (DGL), dietary insulin index (DII), and dietary insulin load (DIL) were measured using a 116-item food frequency questionnaire (FFQ). Multivariate linear regressions were used to associate each dietary score with fasting blood glucose (FBG), triglyceride, total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and systolic and diastolic blood pressure.

Results DGI was significantly associated with serum FBG (β; 0.24, 95% CI; 0.02, 0.46) and triglyceride (β; 0.53, 95% CI; 0.002, 1.06) levels but not TC, HDL, LDL, or blood pressure after adjusting for age, sex, education, marital status, smoking, body mass index, energy intake, physical activity, having other diseases, and family history of diabetes. Neither DGL, DII, nor DIL was significantly associated with each of the cardiometabolic risk factors after controlling for the confounders.

Conclusion A diet with a higher glycemic index accompanied by a higher serum FBG and triglyceride level. Further studies are needed to determine the association of DGL, DII, and DIL with cardiometabolic risk factors.

Keywords Diabetes mellitus · Glycemic index · Insulin · Blood glucose · Blood lipid

Introduction

Type 2 diabetes is a chronic disease manifested in high blood glucose and insulin resistance. The risk of cardiovascular diseases, including ischemic heart disease and stroke, is higher in people with diabetes. They are also at risk of chronic kidney disease, blindness, and amputation [1]. Postprandial hyperglycemia and hyperinsulinemia can increase the risk of cardiovascular disease [2].

Various factors, such as the type of carbohydrate, fiber content, proteins, fats, forms of food, and how they are made, determine the body's glycemic response to foods [3, 4]. The glycemic index is a measure of the glycemic response to targeted food with a fixed amount of carbohydrates compared to reference food with the same amount of carbohydrates. The rise in blood glucose post meal also depends on the grams of carbohydrates consumed, other than the glycemic index. Thereby, glycemic load, calculated by multiplying

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the glycemic index by the grams of carbohydrates in the food, was designed to express the glycemic effects of food quantitatively [5].

Current evidence has shown that diets with a high glycemic index and glycemic load increase the risk of obesity, type 2 diabetes, metabolic syndrome, and cardiovascular diseases [6–9]. By decreasing the glycemic index of the diet, blood glucose and triglyceride decreased, and serum HDL increased [10, 11]. Furthermore, long-term consumption of foods with a high glycemic index increased the need for insulin and induced insulin resistance in people with type 2 diabetes [12]. A high glycemic index diet may worsen other risk factors of cardiovascular disease by increasing the body mass index (BMI) [13].

Carbohydrates primarily influence insulin secretion. But other factors, such as dietary protein and fat, also affect insulin secretion [14]. Therefore, the postprandial insulin response is not necessarily related to the blood glucose concentration because the effect of food on insulin is influenced by other factors such as fructose, certain amino acids, and fatty acids [14]. In this line, dietary insulin index (DII) was proposed that classifies foods based on their insulin response relative to a reference food of equal energy content. Moreover, dietary insulin load (DIL) was calculated based on the insulin index of each food and considering the energy content and frequency of food consumption [15–17]. DII and DIL were introduced as risk factors for insulin resistance [18]. Besides, a study reported that dietary insulin index was related to postprandial glucose [19]. But, a cross-sectional study showed no relationship between the insulin index of the diet and blood glucose in healthy adults [20]. Finnish studies with 22-year follow-ups have shown insulin to be a good predictor of coronary artery disease [21]. But, limited studies have been conducted on the relationship between insulin index and cardiovascular risk factors.

To our knowledge, results are inconsistent and limited regarding the relationship between dietary glycemic index and glycemic load with cardiovascular metabolic risk factors in people with diabetes, and there are no studies that have evaluated the relationship between insulin index and insulin load with cardiovascular, metabolic risk factors in people with diabetes. In addition, different dietary patterns in populations living in various parts of the world with diverse food preferences could affect this relationship. Carbohydrate, especially from white rice and bread, is a dominant part of daily energy intake in the Asian population, including Iran. The amount and type of dietary carbohydrates have a pivotal role in the prevention of cardiovascular disease and controlling of blood glucose [2]. However, very limited studies assessed the relationship between dietary glycemic and insulin indices with the risk factors of cardiovascular diseases in populations where white bread and rice comprise a large part of the diet. White bread is positively related to the risk of diabetes in Japanese women [22]. Besides, white bread has a large share in the dietary glycemic index and load [23, 24]. Therefore, this study was conducted to evaluate the association of dietary glycemic index and load and dietary insulin index and load with cardiometabolic risk factors among people with diabetes.

Methods and materials

This cross-sectional study was carried out based on the baseline data of the Shiraz University of Medical Sciences Employee Health Cohort Study (SUMS EHCS). The ethics committee of Shiraz University of Medical Sciences approved this cross-sectional study (IR.SUMS.SCHEANUT.REC.1400.058). The cohort study was launched in 2017 and looked at the health problems of the employee population. All participants were informed of the purpose and procedure of the study and signed the written form to volunteer for the cohort study.

All employees who visited the EHCS center, aged 25–64 years old, had been diagnosed with diabetes by a medical physician, and used oral hypoglycemic medications were eligible for this cross-sectional study. The exclusion criteria were an incomplete questionnaire, pregnancy, lactation, or following a particular diet. In addition, subjects who took insulin therapy were also excluded. Finally, 88 eligible employees were included in this cross-sectional study.

Data collection

Data were gathered following the published guidelines and procedures of the PERSIAN cohort [25]. Demographic variables and medical histories of the participants were collected using data gathering sheets. The data of age, sex, education, marital status, smoking habits, level of physical activity, having other diseases, and family history of diabetes were obtained for all participants.

A digital scale was used to measure the participants' weight while they were standing in the center of the scale while wearing the lightest clothing possible, to the nearest 0.01 kg. By standing up straight against the wall with the heels, shoulders, and back of the head touching the wall, height was measured to within 0.01 cm using a stadiometer. BMI was computed as weight in kilograms divided by the square of height in meters.

After a fast overnight (8–12 h), blood samples were collected, and serum samples were separated and stored at – 80 °C. Fasting blood glucose (FBG), triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were measured by commercial kits (Pars Azmoon Inc., Tehran, Iran) and Biosystem auto analyzer bt1500 device (Blotecnica instruments, Italy).

The blood pressure, systolic (SBP) and diastolic (DBP) blood pressure, was measured by a trained expert using a Riester precise-N sphygmomanometer. Participants were asked to rest for 10 min before blood pressure measurement. Each person's blood pressure was then measured four times. In this way, blood pressure was measured twice in the brachial vein of the right arm and twice in the left arm.

Dietary intakes and calculation of dietary indices

The dietary intakes of the participants were assessed using a semi-quantitative Food Frequency Questionnaire (FFQ) of 116 points. The validity and reliability of the FFQ were verified in a prior study [26]. On a daily, weekly, monthly, and annual basis, it has been asked how much food was consumed and how often. Nutritionist IV software (version 7.0; N squared computing, Salem, OR, USA) was used to estimate energy and nutrient intakes.

The glycemic index of each food was calculated (glycemic index × available carbohydrate)/total available carbohydrate. The available carbohydrate was total carbohydrate minus fiber. Then, the dietary glycemic index (DGI) was computed as the sum of the glycemic index of all consumed foods. Thereafter, dietary glycemic load (DGL) was calculated (dietary glycemic index × total available carbohydrate)/100. The glycemic index of foods were obtained from international glycemic index tables [27] and Iranian glycemic index table [28]. If the glycemic index of foods was not listed in these tables, they were estimated based on similar foods.

The insulin load of each food was calculated (insulin index × energy content per 1 g × grams of that food consumed). Then, the dietary insulin load (DIL) was computed as the sum of the insulin load of all consumed foods. Thereafter, the dietary insulin index (DII) was calculated (dietary insulin load /total energy intake). The insulin index of foods was obtained from previous studies [15–17]. If the insulin index of foods was not reported, they were estimated based on similar foods.

Statistical analysis

SPSS software (ver. 22 for Windows; SPSS Inc., Chicago, USA) was used to analyze the data. Kolmogorov–Smirnov test was applied to check the normal distribution of the variables. Quantitative data were expressed as mean ± standard deviation (SD) and categorical as number and percentage. Between-group analyses were done by one-way ANOVA test for quantitative variables, and the Pearson chi-square test was used to compare categorical variables among the study groups. The association of DGI, DGL, DII, and DIL with FBG, TG, TC, HDL, LDL, SBP, and DBP was tested using a multivariate linear regression. Furthermore, age, sex, education, marital status, smoking habits, BMI, energy intake, the level of physical activity, having other diseases, and family history of diabetes were adjusted as confounding variables. A p value of 0.05 or less was considered statistically significant.

Results

The mean age of participants was 48.73 ± 5.70 years, and 43.2% of them were female. The characteristics of the study subjects are shown in Table 1. The mean BMI (kg/m^2) was

Table 1 The characteristics of study participants

Variables		
Age*		48.73 ± 5.70
Sex**	Male	50 (56.8)
	Female	38 (43.2)
Marital status**	Single	5 (5.7)
	Married	82 (93.2)
	Divorced	1 (1.1)
Education* (year)		14.07 ± 4.47
Smoking**	Yes	13 (14.8)
	No	75 (85.2)
Body mass index* (kg/m^2)		29.01 ± 4.50
Energy intake* (kcal)		2206.93 ± 685.43
Dietary protein* (g)		75.70 ± 23.81
Dietary carbohydrate* (g)		354.41 ± 125.07
Dietary fat* (g)		60.07 ± 19.41
Dietary fiber* (g)		25.39 ± 9.09
Physical activity level*** (MET.h/week)		942.0 (0.0, 22,320.0)
Family history of diabetes**	Yes	74 (84.1)
	No	14 (15.9)
Having other diseases**	Yes	56 (63.6)
	No	32 (36.4)
Fasting blood glucose* (mg/dl)		151.57 ± 53.17
Triglyceride* (mg/dl)		187.08 ± 120.27
Total cholesterol* (mg/dl)		177.87 ± 35.26
High-density lipoprotein* (mg/dl)		46.79 ± 9.48
Low-density lipoprotein* (mg/dl)		100.76 ± 24.33
Systolic blood pressure* (mmHg)		119.35 ± 14.75
Diastolic blood pressure* (mmHg)		78.15 ± 10.30
Dietary glycemic index score*		85.66 ± 52.41
Dietary glycemic load score*		294.41 ± 259.75
Dietary insulin index score*		37.41 ± 3.88
Dietary insulin load score*		83,249.30 ± 30,116.98

*Data are presented as mean ± SD

**Data are presented as N (%)

***Data are presented as median (min, max)

N (%), number (percentage); kg/m^2, kilogram per square meter; kcal, kilocalorie; g, gram; MET.h/week, metabolic equivalent hours/week; mg/dl, milligrams per deciliter; mmHg, millimeters of mercury

Table 2 The characteristics of study participants across the quartiles of dietary glycemic index and dietary glycemic load

		Dietary glycemic index				*p* value	Dietary glycemic load				*p* value
		Q1	Q2	Q3	Q4		Q1	Q2	Q3	Q4	
N (%)		18 (20.5)	23 (26.1)	26 (29.5)	21 (23.9)	-	19 (21.6)	20 (22.7)	26 (29.5)	23 (26.1)	-
Age* (years)		49.88 ± 5.32	49.86 ± 5.97	47.88 ± 6.26	47.57 ± 4.87	0.38	50.21 ± 5.94	51.55 ± 5.52	47.15 ± 5.31	46.86 ± 5.04	0.01
Sex**	Male	7 (38.9)	10 (43.5)	17 (65.4)	16 (76.2)	0.04	4 (21.1)	8 (40.0)	20 (76.9)	18 (79.3)	< 0.001
	Female	11 (61.1)	13 (56.5)	9 (34.6)	5 (23.8)		15 (78.9)	12 (60.0)	6 (23.1)	5 (21.7)	
Marital status**	Single	1 (5.6)	0 (0)	2 (7.7)	2 (9.5)	0.48	0 (0)	1 (5.0)	2 (7.7)	2 (8.7)	0.58
	Married	17 (94.4)	23 (100)	24 (92.3)	18 (85.7)		19 (100)	19 (95.0)	24 (92.3)	20 (87.0)	
	Divorced	0 (0)	0 (0)	0 (0)	1 (4.8)		0 (0)	0 (0)	0 (0)	1 (4.3)	
Education* (years)		14.83 ± 3.83	15.08 ± 3.77	13.57 ± 3.97	12.95 ± 5.97	0.34	15.15 ± 3.45	14.10 ± 3.74	15.07 ± 4.18	12.04 ± 5.55	0.06
Smoking**	Yes	0 (0)	4 (17.4)	6 (23.1)	3 (14.3)	0.19	1 (5.3)	2 (10.0)	6 (23.1)	4 (17.4)	0.35
	No	18 (100)	19 (82.6)	20 (76.9)	18 (85.7)		18 (94.7)	18 (90.0)	20 (76.9)	19 (82.6)	
Body mass index* (kg/m^2)		28.95 ± 4.53	29.19 ± 4.29	28.99 ± 5.41	28.90 ± 3.69	0.99	27.86 ± 4.05	29.30 ± 4.35	29.07 ± 4.76	29.64 ± 4.77	0.62
Energy intake* (kcal)		2029.54 ± 708.79	2019.27 ± 541.78	2296.30 ± 817.00	2453.88 ± 562.29	0.10	1382.43 ± 227.89	1973.10 ± 271.20	2527.54 ± 449.37	2728.95 ± 692.27	< 0.001
Dietary protein* (g)		72.31 ± 24.52	68.76 ± 19.67	79.75 ± 28.28	81.20 ± 20.25	0.24	50.35 ± 13.32	68.54 ± 14.22	88.05 ± 20.00	88.91 ± 22.43	< 0.001
Dietary carbohydrate* (g)		311.33 ± 119.40	320.10 ± 90.24	377.89 ± 155.27	399.85 ± 104.51	0.05	207.39 ± 28.02	309.13 ± 42.23	406.25 ± 77.07	456.65 ± 135.24	< 0.001
Dietary fat* (g)		62.50 ± 22.95	57.02 ± 18.58	56.88 ± 19.71	65.27 ± 16.36	0.38	42.82 ± 16.37	57.22 ± 15.67	68.36 ± 16.75	67.42 ± 18.36	< 0.001
Dietary fiber* (g)		28.83 ± 11.33	23.13 ± 7.94	24.27 ± 10.20	26.32 ± 5.68	0.20	17.29 ± 5.32	23.79 ± 8.28	29.95 ± 9.43	28.32 ± 7.15	< 0.001
Physical activity level* (MET.h/week)		2193.16 ± 2908.71	3860.65 ± 4988.79	2372.88 ± 4292.39	5082.42 ± 6824.04	0.20	3085.26 ± 4421.70	2036.45 ± 3708.89	2840.30 ± 3821.97	5369.60 ± 7027.18	0.14
Family history of diabetes**	Yes	14 (77.8)	21 (91.3)	22 (84.6)	17 (81.0)	0.66	17 (89.5)	18 (90.0)	20 (76.9)	19 (82.6)	0.58
	No	4 (22.2)	2 (8.7)	4 (15.4)	4 (19.0)		2 (10.5)	2 (10.0)	6 (23.1)	4 (17.4)	
Having other diseases**	Yes	12 (66.7)	13 (56.5)	16 (61.5)	15 (71.4)	0.76	13 (68.4)	11 (55.0)	15 (57.7)	17 (73.9)	0.51
	No	6 (33.3)	10 (43.5)	10 (38.5)	6 (28.6)		6 (31.6)	9 (45.0)	11 (42.3)	6 (26.1)	
Fasting blood glucose* (mg/dl)		146.84 ± 45.35	137.42 ± 34.97	150.07 ± 48.33	172.97 ± 74.49	0.15	146.32 ± 51.26	140.72 ± 41.16	145.61 ± 34.06	172.08 ± 75.05	0.19
Triglyceride* (mg/dl)		169.51 ± 72.15	166.09 ± 82.10	176.50 ± 121.85	238.24 ± 169.85	0.16	154.88 ± 83.51	153.41 ± 55.46	192.43 ± 87.55	236.92 ± 188.61	0.07
Total cholesterol* (mg/dl)		171.05 ± 37.97	179.00 ± 38.22	176.54 ± 36.38	184.13 ± 28.89	0.71	189.96 ± 39.40	161.40 ± 32.80	175.82 ± 35.56	184.53 ± 29.24	0.05
High-density lipoprotein* (mg/dl)		47.71 ± 10.46	50.61 ± 9.83	45.12 ± 7.19	43.90 ± 9.86	0.08	50.14 ± 10.99	48.92 ± 8.34	45.55 ± 9.19	43.58 ± 8.62	0.09
LDL density lipoprotein* (mg/dl)		95.44 ± 27.92	100.45 ± 27.05	99.46 ± 22.67	107.27 ± 19.84	0.49	109.93 ± 25.64	88.73 ± 24.35	98.91 ± 24.84	105.75 ± 18.88	0.03
Systolic blood pressure* (mmHg)		114.72 ± 11.44	119.82 ± 15.40	121.57 ± 18.17	120.04 ± 11.64	0.49	116.84 ± 13.26	116.70 ± 14.71	119.11 ± 15.67	124.00 ± 14.71	0.32
Diastolic blood pressure* (mmHg)		74.66 ± 8.45	79.00 ± 10.59	79.11 ± 12.42	79.04 ± 8.43	0.46	76.73 ± 6.47	74.75 ± 11.26	78.11 ± 10.90	82.34 ± 10.51	0.09
Dietary glycemic index score*		55.38 ± 2.12	60.52 ± 1.30	67.61 ± 5.26	161.49 ± 62.40	< 0.001	59.56 ± 5.49	60.27 ± 4.24	68.05 ± 14.28	149.21 ± 69.47	< 0.001
Dietary glycemic load score*		148.80 ± 61.31	172.28 ± 51.65	241.54 ± 99.38	618.45 ± 353.41	< 0.001	107.64 ± 17.53	167.21 ± 16.35	243.55 ± 31.98	616.81 ± 329.57	< 0.001
Dietary insulin index score*		35.51 ± 4.16	37.42 ± 3.53	37.90 ± 3.42	38.40 ± 4.21	0.10	35.68 ± 4.84	36.93 ± 3.05	37.31 ± 3.01	39.35 ± 3.90	0.01
Dietary insulin load score*		72,221.45 ± 27,073.08	75,904.54 ± 13,014.70	87,811.32 ± 35,689.99	95,097.77 ± 28,315.51	0.05	48,722.66 ± 7262.53	72,790.74 ± 11,068.51	94,343.18 ± 18,498.00	10,8324.78 ± 33,426.40	< 0.001

*Data are presented as mean ± SD

**Data are presented as *N* (%)

Q, quartiles; *N* (%), number (percentage); kg/m^2, kilogram per square meter; kcal, kilocalorie; g, gram; MET.h/week, metabolic equivalent hours/week; mg/dl, milligrams per deciliter; mmHg, millimeters of mercury

29.01 ± 4.50. Moreover, 84.1% of the participants had a family history of diabetes. The mean daily energy intake was 2206.93 ± 685.43 kilocalories. The mean carbohydrate, protein, fat, and fiber intakes were 354.41 ± 125.07 g, 75.70 ± 23.81 g, 60.07 ± 19.41 g, and 25.39 ± 9.09 g, respectively. The cardiometabolic risk factors of the study participants were obtained as follows: FBS, 151.57 ± 53.17 mg/dl; TG, 187.08 ± 120.27 mg/dl; TC, 177.87 ± 35.26 mg/dl; HDL, 46.79 ± 9.48 mg/dl; LDL, 100.76 ± 24.33 mg/dl; SBP, 119.35 ± 14.75 mmHg; and DBP, 78.15 ± 10.30 mmHg.

Tables 2 and 3 shows the characteristics of the participants across the quartiles of DGI, DGL, DII, and DIL. The younger subjects were in higher quartiles of DGL ($p = 0.01$) and DIL ($p = 0.03$). By increasing the quartiles of DGI ($p = 0.04$), DGL ($p < 0.001$), and DIL ($p = 0.001$), the number of males increased and the number of females decreased. An increasing trend of energy intake, dietary protein, carbohydrate, fat, and fiber was seen with increasing quartiles of both DGL and DIL ($p < 0.001$). However, a direct and significant trend was seen between dietary carbohydrates and quartiles of DGI ($p = 0.05$) and DII ($p = 0.007$).

As shown in Table 4, the fully adjusted model of linear regression analysis showed a direct association between DGI and serum FBS and TG levels. DGL was directly associated with serum FBS and TG levels and indirectly associated with serum HDL levels; however, it did not remain statistically significant after adjusting for age, sex, energy intake, physical activity, education level, marital status, smoking, family history of diabetes, having other diseases, and BMI. Both DGI and DGL were not significantly associated with TC, LDL, SBP, and DBP. In addition, no significant association was found between DII or DIL and FBS, TG, TC, HDL, LDL, SBP, and DBP levels.

Discussion

The present study revealed that DGI was positively associated with serum FBG and TG levels after adjustment for confounding variables. However, DGI was not associated with other cardiometabolic risk factors, including TC, HDL, LDL, SBP, and DBP. No associations were also found between DGL, DII, and DIL with all measured cardiometabolic risk factors.

DGI was directly associated with serum FBG levels. Similar findings reported that fasting and postprandial glucose were lower in subjects with diabetes and obesity who had a diet with a low glycemic index and glycemic load [29, 30]. Moreover, diets with a low glycemic index were associated with lower glycated hemoglobin levels in people with type 1 and type 2 diabetes [29, 31, 32]. The carbohydrates in high-glycemic index foods are digested and absorbed more easily than the carbohydrates in low-glycemic index foods, which cause higher postprandial glucose. On the other hand, the carbohydrates in low-glycemic index foods digest more slowly than those in high-glycemic index foods and gradually increase the blood glucose [33]. Over time, frequent consumption of high-glycemic index meals causes high insulin levels, increased insulin resistance, and the degradation of the beta cells in the pancreas [33]. Therefore, a high FBG level would appear. In this study, DGL was not associated with FBG after controlling for confounders. However, a non-significant increasing trend of FBG was seen by increasing the quartiles of DGL. This study revealed no association between DII and DIL with FBG. In contrast, Mozaffari et al. showed that higher DIL was associated with higher FBG levels among elderly men [34]. However, DII and DIL were not associated with HbA1C in another study among healthy subjects [20]. Moreover, higher FBG levels in females and lower levels in males were reported in adults in the higher quartile of DII [35]. Since these studies were conducted on healthy subjects, additional research on people with diabetes is required to clarify this hypothesis.

This study showed that the increase in DGI was associated with the rise in serum TG levels in people with diabetes after adjusting for confounders. In agreement with our results, the Tehran glucose and lipid study showed that DGI was directly associated with serum TG levels among 2457 healthy subjects [30]. Similar results were reported by other studies among healthy, normal, or overweight subjects [36, 37]. High-glycemic index foods induce lipogenic enzymes that lead to increased plasma lipid and fat storage. It could stimulate acetyl-CoA carboxylase and fatty acid synthesis [38]. Moreover, fatty acid oxidation will be attenuated by inhibiting carnitine palmitoyltransferase I [38]. Although DGL was not associated with TG after controlling for confounders, in our study, a non-significant increasing trend of serum TG levels was seen by increasing the quartiles of DGL. We found that serum TG level was not associated with DII or DIL. The same result was also reported in the elderly population [34]; however, a higher TG level was observed in obese subjects who were in the higher quintile of DII compared to the lower quintile [20]. DII and DIL are influenced by protein and fat other than carbohydrates. Moreover, the type of amino acids and the length of fatty acids, as well as their saturation level, could affect the insulin index and load [39]. Since serum TG levels are more sensitive to carbohydrates, they might be more sensitive to the glycemic index compared to the insulin index.

Our results failed to find a significant association between each of the dietary indices (DGI, DGL, DII, and DIL) and serum TC, HDL, and LDL levels after controlling for confounders. However, an inverse association was seen between DGI and DGL with serum HDL in the unadjusted model of linear regression analysis. Recent studies showed that DGI and/or DGL were inversely related to

Table 3 The characteristics of study participants across the quartiles of dietary insulin index and dietary insulin load scores

		Dietary insulin index					Dietary insulin load				
		Q1	Q2	Q3	Q4	*p* value	Q1	Q2	Q3	Q4	*p* value
N (%)		16 (18.2)	23 (26.1)	24 (27.30	25 (28.4)	-	15 (17.0)	26 (29.5)	22 (25.0)	25 (28.4)	-
Age* (years)		52.12 ± 6.31	47.47 ± 5.68	48.00 ± 5.27	48.44 ± 5.17	0.06	50.86 ± 5.66	49.84 ± 6.01	49.00 ± 6.02	46.08 ± 4.24	0.03
Sex**	Male	9 (56.3)	12 (52.2)	12 (50.0)	17 (68.0)	0.58	3 (20.0)	12 (46.2)	14 (63.6)	21 (84.0)	0.001
	Female	7 (43.8)	11 (47.8)	12 (50.0)	8 (32.0)		12 (80.0)	14 (53.8)	8 (36.4)	4 (16.0)	
Marital status**	Single	1 (6.3)	0 (0)	2 (8.3)	2 (8.0)	0.58	1 (6.7)	0 (0)	1 (4.5)	3 (12.0)	0.44
	Married	15 (93.8)	22 (95.7)	22 (91.7)	23 (92.0)		14 (93.3)	25 (96.2)	21 (95.5)	22 (88.0)	
	Divorced	0 (0)	1 (4.3)	0 (0)	0 (0)		0 (0)	1 (3.8)	0 (0)	0 (0)	
Education* (years)		13.93 ± 4.91	14.00 ± 4.61	15.04 ± 3.88	13.32 ± 4.67	0.61	14.33 ± 3.39	14.46 ± 4.14	14.77 ± 5.01	12.92 ± 4.88	0.49
Smoking**	Yes	3 (18.8)	2 (8.7)	3 (12.5)	5 (20.0)	0.67	0 (0)	4 (15.4)	2 (9.1)	7 (28.0)	0.08
	No	13 (81.3)	21 (91.3)	21 (87.5)	20 (80.0)		15 (100)	22 (84.6)	20 (90.9)	18 (72.0)	
Body mass index* (kg/m^2)		28.15 ± 5.19	27.76 ± 4.32	29.06 ± 3.64	30.68 ± 4.67	0.12	27.74 ± 4.49	28.78 ± 4.03	28.85 ± 4.34	30.16 ± 5.07	0.41
Energy intake* (kcal)		1941.18 ± 623.23	2189.19 ± 492.42	2190.84 ± 628.47	2408.79 ± 877.18	0.20	1382.46 ± 275.03	1793.49 ± 225.55	2330.66 ± 237.13	3022.72 ± 489.35	< 0.001
Dietary protein* (g)		72.62 ± 28.35	76.41 ± 19.34	72.57 ± 18.86	80.03 ± 28.85	0.68	49.42 ± 14.22	62.04 ± 11.14	83.02 ± 17.21	99.24 ± 16.99	< 0.001
Dietary carbohydrate* (g)		275.25 ± 98.32	341.76 ± 81.06	361.73 ± 114.43	409.69 ± 156.59	0.007	199.51 ± 25.30	286.80 ± 35.47	366.12 ± 32.56	507.36 ± 98.23	< 0.001
Dietary fat* (g)		66.15 ± 18.94	63.75 ± 18.20	56.87 ± 16.82	55.86 ± 22.36	0.24	46.33 ± 19.90	49.61 ± 13.93	66.17 ± 12.95	73.82 ± 17.83	< 0.001
Dietary fiber* (g)		21.45 ± 7.36	26.24 ± 9.12	26.85 ± 10.05	25.73 ± 8.92	0.28	15.60 ± 5.04	21.81 ± 4.90	28.10 ± 7.36	32.61 ± 8.82	< 0.001
Physical activity level* (MET.h/week)		2491.68 ± 3808.35	2916.69 ± 6017.27	3623.75 ± 4718.23	4111.08 ± 5175.05	0.74	2751.60 ± 3664.06	3746.34 ± 6474.16	1870.22 ± 3118.85	4674.96 ± 5242.68	0.26
Family history of diabetes**	Yes	14 (87.5)	20 (87.0)	18 (75.0)	22 (88.0)	0.56	14 (93.3)	23 (88.5)	17 (77.3)	20 (80.0)	0.49
	No	2 (12.5)	3 (13.0)	6 (25.0)	3 (12.0)		1 (6.7)	3 (11.5)	5 (22.7)	5 (20.0)	
Having other diseases**	Yes	12 (75.0)	14 (60.9)	12 (50.0)	18 (72.0)	0.30	11 (73.3)	13 (50.0)	16 (72.7)	16 (64.0)	0.32
	No	4 (25.0)	9 (39.1)	12 (50.0)	7 (28.0)		4 (26.7)	13 (50.0)	6 (27.3)	9 (36.0)	
Fasting blood glucose* (mg/dl)		157.47 ± 42.58	157.81 ± 50.38	153.87 ± 57.78	139.84 ± 58.12	0.62	144.26 ± 49.76	157.84 ± 48.76	143.22 ± 49.87	156.77 ± 63.09	0.70
Triglyceride* (mg/dl)		206.34 ± 171.61	165.57 ± 68.52	166.36 ± 78.38	214.44 ± 148.12	0.37	129.98 ± 49.88	193.71 ± 86.07	162.79 ± 73.09	235.83 ± 183.01	0.03
Total cholesterol* (mg/dl)		179.38 ± 38.09	177.01 ± 31.67	177.23 ± 35.69	178.32 ± 38.16	0.99	180.29 ± 40.97	180.77 ± 35.55	175.84 ± 31.39	175.18 ± 36.39	0.93
High-density lipoprotein* (mg/dl)		46.64 ± 13.01	48.40 ± 8.07	46.88 ± 8.87	45.33 ± 8.95	0.74	50.71 ± 11.14	47.14 ± 9.31	46.34 ± 8.81	44.49 ± 8.93	0.25
LDL density lipoprotein* (mg/dl)		100.77 ± 25.71	100.27 ± 23.53	104.81 ± 25.20	97.32 ± 24.26	0.76	103.94 ± 27.73	102.23 ± 24.07	103.17 ± 24.64	95.21 ± 22.73	0.60
Systolic blood pressure* (mmHg)		118.62 ± 13.51	115.78 ± 12.54	118.16 ± 13.92	124.24 ± 17.50	0.23	117.86 ± 13.23	115.88 ± 11.90	118.36 ± 16.85	124.72 ± 15.67	0.17
Diastolic blood pressure* (mmHg)		77.50 ± 7.78	76.08 ± 11.74	77.41 ± 9.92	81.20 ± 10.57	0.35	77.66 ± 6.53	74.23 ± 6.84	78.09 ± 14.41	82.60 ± 9.59	0.03
Dietary glycemic index score*		84.49 ± 57.11	78.01 ± 46.67	81.68 ± 34.34	97.26 ± 67.66	0.60	61.12 ± 6.04	80.80 ± 39.43	89.28 ± 54.58	102.25 ± 70.77	0.10
Dietary glycemic load score*		235.27 ± 272.07	242.25 ± 175.63	287.81 ± 207.42	386.59 ± 339.08	0.17	109.19 ± 22.15	212.77 ± 118.31	300.51 ± 205.41	485.09 ± 355.29	< 0.001
Dietary insulin index score*		31.67 ± 2..62	35.78 ± 0.76	38.23 ± 0.81	41.78 ± 2.01	< 0.001	33.87 ± 4.80	37.35 ± 2.79	36.88 ± 2.82	40.05 ± 3.26	< 0.001
Dietary insulin load score*		61,643.21 ± 21,485.92	78,374.98 ± 17,997.43	83,749.45 ± 23,992.86	101,081.41 ± 38,541.01	< 0.001	45,788.07 ± 5170.86	66,556.74 ± 5938.86	85,541.66 ± 6746.91	121,069.30 ± 22,850.17	< 0.001

*Data are presented as mean ± SD

**Data are presented as *N* (%)

Q, quartiles; N (%), number (percentage); kg/m^2, kilogram per square meter; kcal, kilocalorie; g, gram; MET.h/week, metabolic equivalent hours/week; mg/dl, milligrams per deciliter; mmHg, millimeters of mercury

Table 4 Multivariate-adjusted linear regression analysis of cardiometabolic risk factors associated with the scores of dietary glycemic index, dietary glycemic load, dietary insulin index, and dietary insulin load

		Dietary glycemic index	Dietary glycemic load	Dietary insulin index	Dietary insulin load
Fasting blood glucose (mg/dl)	Unadjusted	0.30 (0.1, 0.51)	0.04 (0.001, 0.08)	−0.61 (−3.55, 2.31)	0.00002 (0.0, 0.0)
	Adjusted*	0.24 (0.02, 0.46)	0.03 (−0.01, 0.09)	−1.98 (−5.00, 1.04)	−0.001 (−0.002, 0.0)
Triglyceride (mg/dl)	Unadjusted	0.62 (0.15, 1.09)	0.13 (0.03, 0.22)	3.78 (−2.81, 10.37)	0.001 (0.0, 0.002)
	Adjusted*	0.53 (0.002, 1.06)	0.10 (−0.02, 0.23)	1.01 (−6.24, 8.27)	−0.00001 (−0.003, 0.003)
Total cholesterol (mg/dl)	Unadjusted	0.03 (−0.11, 0.17)	0.003 (−0.02, 0.03)	−0.73 (−2.67, 1.21)	−0.00003 (0.0, 0.0)
	Adjusted*	0.11 (−0.04, 0.28)	0.02 (−0.01, 0.06)	−0.25 (−2.43, 1.92)	−0.00002 (−0.001, 0.001)
High-density lipoprotein (mg/dl)	Unadjusted	−0.03 (−0.07, 0.001)	−0.008 (−0.01, −0.001)	−0.34 (−0.86, 0.17)	−0.00006 (0.0, 0.0)
	Adjusted*	−0.01 (−0.05, 0.02)	−0.001 (−0.01, 0.008)	−0.06 (−0.57, 0.44)	0.00004 (0.0, 0.0)
Low-density lipoprotein (mg/dl)	Unadjusted	0.02 (−0.07, 0.12)	0.002 (−0.02, 0.02)	−0.60 (−1.94, 0.73)	−0.00005 (0.0, 0.0)
	Adjusted*	0.07 (−0.03, 0.19)	0.02 (−0.009, 0.04)	−0.24 (−1.76, 1.28)	−0.00002 (−0.001, 0.001)
Systolic blood pressure (mmHg)	Unadjusted	0.03 (−0.02, 0.09)	0.009 (−0.003, 0.02)	0.70 (−0.09, 1.50)	0.0 (0.0, 0.0)
	Adjusted*	−0.01 (−0.07, 0.05)	−0.003 (−0.02, 0.01)	0.30 (−0.53, 1.12)	0.0 (0.0, 0.001)
Diastolic blood pressure (mmHg)	Unadjusted	0.02 (−0.02, 0.06)	0.007 (−0.001, 0.01)	0.48 (−0.07, 1.04)	0.0 (0.0, 0.0)
	Adjusted*	−0.01 (−0.05, 0.02)	−0.003 (−0.01, 0.006)	0.02 (−0.50, 0.55)	0.00008 (0.0, 0.0)

Data are presented as beta (95% CI)

mg/dl, milligrams per deciliter; mmHg, millimeters of mercury

*Adjusted for age, sex, energy intake, physical activity level, education, marital status, smoking, family history of diabetes, having other diseases, and body mass index

serum HDL levels in obese and diabetic subjects [30, 31]. However, findings are inconsistent regarding the association of both DII and DIL with serum HDL and LDL levels [20, 34]. Some high-glycemic foods, such as fruits, are rich in fiber, antioxidants, and phytochemicals, which might improve blood lipid [40] and attenuate the role of the glycemic and insulinemic indices of the foods. In addition, this study demonstrated that neither DGI, DGL, DII, nor DIL was significantly associated with both systolic and diastolic blood pressure. As we mentioned earlier, some high-glycemic foods as well as some foods with a high insulin index, such as yogurt, fruits, skim milk, etc., are components of the DASH diet that are recommended to be used more and have antihypertensive and/or anti-inflammatory properties [33, 40].

All participants used oral hypoglycemic agents and used medication to control serum TG, cholesterol, and blood pressure if abnormal levels were seen. Medication may interfere with the association of DGI, DGL, DII, and DIL with cardiometabolic risk factors. Moreover, considering the recommendation of the American Diabetic Association [41], the serum FBG and TG levels were not controlled within the normal range among our study subjects, but the mean levels of TC, LDL, HDL, and blood pressure were, which may interfere with the results.

Furthermore, different dietary patterns among people living around the world may cause inconsistent results between studies. For instance, carbohydrates comprise a large percentage of daily energy intake in Iran, more than 60% of which was also observed in this study.

In our study, no significant association was seen between DII or DIL and glycemic control or each of the cardiometabolic risk factors among people with diabetes. It was assumed that DII and DIL might not be sensitive indices in people with diabetes due to the high insulin levels and insulin resistance in these subjects and that insulin secretion may be disturbed in response to the diet. Moreover, DII in our study was not at a high level. Thus, it might not change cardiometabolic risk factors. Few studies have assessed the association of DII or DIL with cardiometabolic risk factors, which are mostly conducted on healthy or obese subjects. Further studies need to be done among people with diabetes.

This study has some limitations. First, no causal relationship could be found in this study. Second, the small sample size was another limitation. Third, published glycemic and insulin index values for many food items included in Iranian foods are limited. Fourth, food processing, cooking method and time, and food storage could affect the glycemic index of the food that was not assessed in this study. Fifth, no serum insulin levels were measured, and no insulin resistance was determined. However, the strengths of this study were controlling for a broad range of potential confounders and excluding the subjects who used insulin therapy. In future studies with a large sample size, stratified analysis based on age and gender is proposed.

Conclusion

Higher serum FBG and TG levels were associated with a higher DGI among people with diabetes. However, serum TC, HDL, and LDL levels as well as blood pressure were not associated with DGI. In addition, DGL, DII, and DIL were not associated with each of the cardiometabolic risk factors. More studies with a larger sample size need to be done regarding DGI/DGL and especially DII/DIL and the cardiometabolic risk factors among people with diabetes.

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Author contribution ZH and SJM conceived and planned the study; ZH analyzed the data, and all authors contributed to the interpretation of the results; ZH and KG wrote the manuscript in consultation with SJM.

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Availability of data and materials No additional materials.

Declarations

Consent for publication and ethical approval The ethics committee of Shiraz University of Medical Sciences approved this cross-sectional study (IR.SUMS.SCHEANUT.REC.1400.058). All participants were informed of the purpose and procedure of the study and signed the written form to volunteer for the cohort study.

Conflict of interest The authors declare no competing interests.

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ORIGINAL ARTICLE

Inflammatory potential of the diet is associated with psychological stress in adults with type 2 diabetes: a methodological approach of e-Health

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Abstract

Objective We studied the presence of psychological stress in patients with type 2 diabetes (T2D) and if could be attributed to the consumption of a pro-inflammatory diet. We evaluated the inflammatory potential of the habitual Mexican diet, addressed by tools with an approach to collecting information on e-Health.

Methods In this cross-sectional analytic study of 238 Mexican adults with T2D, the profile of the inflammatory diet was obtained by the Dietary Inflammatory Index (DII), and the presence of psychological stress by the Diabetes Distress Scale-17 (DSS) was assessed. Multivariable logistic regression analysis was performed to estimate the association between diabetes stress and DII score. Sensitivity analysis was performed by Energy–Density Dietary Inflammatory Index (E-DII).

Results We demonstrated that there is an association between a profile of stress and high-inflammatory values of the DII score after adjustment for potential confounders (OR 2.40, 95% CI 1.2, 4.6).

Conclusion Using e-Health through web-based tools to collect information showed benefits of the application as a method of dietary assessment. We provide evidence showing that better values of the DII score and physical activity may play a protective role against the presence of psychological stress; DII and E-DII scores qualify and label habitual diet into pro and anti-inflammatory and are associated with psychological stress in T2D.

Keywords Chronic inflammation · Chronic stress · Dietary assessment · Dietary surveys · Psychosocial factors

Introduction

Type 2 diabetes (T2D) is a global disease, and Mexico is one of the countries with the highest prevalence [1]. The treatment of chronic diseases involves adjustment and change of a series of behavioral patterns, generally affecting lifestyle and choices about food and meals associated with inflammation generating psychological stress [2]. In general, psychological stress could be developed in response to the environment, including foods and meals that people could access and the emotional stress they endure [3]. Evidence has demonstrated that in T2D, diet and inflammatory status could influence the presence of stress [4], which may extend beyond it. Recently, we have shown that the diet possesses pro or anti-inflammatory properties [5]. It has been shown that the immune system is resynchronized by feeding [6], and immune responses are also orchestrated by an inflammatory diet and exhibit effects on intermediaries that coordinate several innate immune cells such as macrophages, monocytes, and neutrophils that are capable of producing glucocorticoids [7]; Consumption of pro-inflammatory dietary compounds such as sweetened drinks, sweet cereals, and sweet snacks and desserts has shown a relationship with cortisol levels [8].

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The high-level scores are associated with higher inflammatory status in cohort studies. A pro-inflammatory diet has been associated with T2D among adult Mexicans [8]. Additionally, stressful environments and large variability in quick-service food solutions represent the Mexican common lifestyle and provide information to characterize profile inflammatory [9].

The e-Health is an emergent technology tool for application in methods of dietary assessment. Studies have confirmed its reliability [10, 11]. Nowadays, it is possible to build web-based tools to evaluate the profile of psychological stress from paper-based tools [12]. Hence, it is possible to use web-dietary surveys to obtain a Dietary Inflammatory Index (DII®) [13] and an Energy–Density Dietary Inflammatory Index (E-DII™) [14] by computing scores of the inflammatory potential of the diet and characterizing the habitual diet. These forms represent a versatile approach, saving time, and costs [15].

We hypothesized that T2D patients with a pro-inflammatory diet were more likely to suffer psychological stress. Indeed, lifestyle such as health behaviors and food choices could be related to this condition. Investigating some domains of lifestyle and the profile of stress is needed to further understand the complex links between psychological stress and T2D [16].

For this purpose, we decided to explore the inflammatory profile of the Mexican habitual diet and its association with a profile of stress. Thus, the main objective of our study was to evaluate the inflammatory potential of the diet in the habitual Mexican diet and if there is a relation between the presence of psychological stress addressed by tools with an approach to collecting information on e-Health in Mexican adults with T2D.

Materials and methods

Study design

Mexican adults participated in this cross-sectional analytical study in an outpatient clinic-based sample physician-diagnosed with T2D. This was a convenience sample of adult population. We divided them into two groups according to the type of recruitment: (a) We used a community-based approach which entailed several different strategies to recruit participants (e.g., use of social media) and (b) patients of Diabetes Clinic at the "Adolfo López Mateos" Medical Center were invited. Patients were recruited from February to July 2022. The study included 230 participants.

The inclusion criteria for this study were as follows: (1) males and females, aged + 18; (2) diagnosed with type 2 diabetes for at least 1 month or more; (3) Mexican nationality and living in Mexico; (4) under medical care for diabetes in Mexico; (5) able to read and write Spanish to complete the forms, questionnaires, and tests; (6) access to the internet website; and (7) acceptance to participate in this study. The exclusion criteria were based on self-reports from participants of the following: (1) physical and/or mental conditions that obstruct participation; (2) incapacity to obtain reliable information; and (3) complications of T2D that interfered with or modified medical treatment as renal disease or replacement therapy.

Data collection: e-Health

The tool e-Health was used for data collection through a website with web-based questionnaires/tests from paper-based tools. The patients were instructed on how to access online to fill out the questionnaires/tests. Each patient's data was collected with the help of a major questionnaire divided into 3 sections: identification data, reported dietary data, and tests. Participants who did not know how to fill in were interviewed through video call. They received regular communication from the team through newsletters, reminder emails, and reminder texts for completion. Survey data collector kept records in the cloud, computing them until their analyses. Acceptability of the website was measured by the total of invitations, time using the website, incomplete questionaries, and rejection to participate in the study [17].

Obtaining dietary information and creating the Dietary Inflammatory Index

We evaluated dietary intakes based on a validated paper-based Food Frequency Questionnaire (FFQ) migrated to web-based [18, 19]; validity of a web-based FFQ has previously been reported [20]. We constructed, with the use of images for portion size estimation and multiple options, a web-based questionnaire which contained 160 food items combining the characteristics of a typical Mexican diet with multiple possible answers, divided into 8 sections. Possible answers indicated the frequency of consumption of each food in relative frequency (never, almost, and always) and absolute frequency (times per month, week, day). Kind and type of meals and foods were evaluated by quantifiers (e.g., cups, glasses, plates, portions) to obtain the amount of the food consumed. We applied a 24-h recall from three different days to contrast information. Dietary intake and nutrient composition were analyzed by ESHA's Food Processor® Nutrition Analysis software version 11.2.23 (ESHA Research©, Oregon, USA). Additionally, we evaluated the composition of Mexican foods through the Database of Mexican Foods Composition ("BAM") version 18.1.1(INSP, Mexico) [21] and polyphenol intake using the USDA Database for the Flavonoid Content of Selected Foods Release 3.0 [22] in combination with the Phenol Explorer Database version 3.6 [23].

Calculation of the DII score was obtained by computing the amounts of nutrients collected using the FFQ and transformed into intakes of food parameters from the individual diet composition. The DII development has been described elsewhere [13]. As result of calculation of the DII, we obtained individual scores and the inflammatory potential of the diet. According to composite global database and global scores, the scale of the DII score of the maximal pro-inflammatory diet was interpreted at + 7.98, the maximal anti-inflammatory DII score was interpreted at − 8.87, and the neutral/transition effect was at + 0.23.

Tests applied on study population

Profile of psychological stress

We evaluated stress variables, with measurements made with two instruments, the first one assesses perceived stress (PSS-14) [24], interpreted as very low stress (0 to 15 points) and high stress (16 to 21 points); the second tool evaluates the stress caused by diabetes and types of distress, the Diabetes Distress Scale-17 (DSS), that pre-establishes items from four domains of diabetes-related distress: emotional burden distress subscale, physician-related distress subscale, regimen-related distress subscale, and diabetes-related interpersonal distress subscale [12]. We obtained interpretations from subscale scores. The total score of DSS was interpreted as psychological stress and categorized as low-moderate stress (≤ 2.9 mean item score) and high stress (≥ 3.0 mean item score) [25]. Spanish versions of the instruments were validated in Mexican people living with T2D previously [26, 27].

Assessing self-management and quality of life

The Diabetes Self-Management Questionnaire (DSMQ) was applied for glycemic control assessment, and the subscale glucose management from DSMQ was utilized. Glucose management and interpretation were categorized low effective management (scale ranging from 0 to 5) and more effective management (scale ranging from 6 to 10). The questionnaire was designed to assess self-care behaviors which can be related to the measure of HbA1c [28]. For the assessment of adherence to medical treatment, we tested with the 8-item Morisky Medication Adherence Scale (MMAS-8); adherence is determined according to the final score (total sum of 8 points) and categorized as adherence (total of 8 points) and no adherence (< 8 total points). We evaluated lifestyle domains utilizing the Instrument to measure lifestyle of type 2 diabetes mellitus patients (*IMEVID).* This tool explored barriers to diabetes self-management such as physical activity, smoking, type of diet, cooking capacity, and effort to eat well (also called the "healthy eater" effect due to the intention of careful, health-conscious people to choose meals). The total scores were obtained; the results were categorized into a rating system as favorable (≥ 80 total points) and unfavorable lifestyle (≤ 80 total points). These tools were validated in the Mexican population with T2D [29–31].

Statistical analyses

A descriptive analysis of the socio-demographic characteristics of the study population was performed, and we analyzed the differences by type of recruitment. Continuous variables are described in terms of averages and standard deviations (mean ± SD) or median (minimum–maximum); categorical variables were described by numbers and percentages. The χ^2 test was used for interpreting categorical variables and Student's *t* test was for continuous variables. Spearman's correlation coefficient calculated the relation between diet and inflammation and stress response.

We constructed a dichotomous variable for analysis of the DII score, we divided the data into low-inflammatory scores (≤ 1.0) and high-inflammatory scores (> 1.0), and the χ^2 test was used to examine associations between stress variables and the inflammatory diet. We used bivariate analysis to estimate the association between diabetes stress and DII score; we used a simple univariable (unadjusted) and multivariable logistic regression analysis adjusted for predictors of stress (age, sex, physical activity, smoking, and body mass index (BMI)). To assess possible effect modification, analyses stratified by sex and age were performed. Logistic regression analyses were used to calculate ORs and 95% CIs of DII concerning to diabetes stress. Two-tailed *p* values were utilized, where a *p* value less than 0.05 was deemed statistically significant. Analyses were performed using IBM® SPSS® Statistics software version 25.0 and Graphpad© Prism software version 9.4.1 for drawing plots and DAGitty software version 3.0 for drawing and analyzing the acyclic graph.

Sensitivity analysis: comparison with the Energy–Density Dietary Inflammatory Index

E-DII was created to improve the prediction of observed relations between overall consumption of dietary energy and nutrient intakes and densities that differ among the studied population to determine the diet's overall inflammatory potential [14]. The energy-adjusted from every food parameter was expressed per thousand kilocalories (1000 kcal). The following 22 food parameters available for E-DII were used: carbohydrate; fiber; protein; total fat; saturated fat; monounsaturated fat; polyunsaturated fat; n-3 fatty acids; n-6 fatty acids; cholesterol; vitamins A, B1, B2, B3, B6, B12, C, D, and E; beta-carotene; folate; magnesium; iron; selenium; zinc; alcohol; and caffeine.

To explore whether E-DII provided a better adjustment to our multivariable-adjusted mixed model, we performed

Spearman's correlations between DII and E-DII, and we constructed E-DII quintiles; the ANOVA test was used to evaluate differences across quintiles, and the χ^2 test was used to examine the distribution of qualitative variables over E-DII quintiles. Finally, we used EB subscale and E-DII potential confounding factors in the stratified analysis.

Results

Study population and outcomes of data collection: e-Health

A total of 238 participants with T2D constituted our study population: 100 (42%) males and 138 (58%) females. The average age was 55.5 ± 12.1, BMI was 29.5 ± 5.5 kg/m^2, and duration of diabetes was 10.5 ± 8.8 years. The number of participants who were treated with oral-antidiabetic medication and insulin was 130 (38.1%), and 61 (25.6%) subjects consumed metformin. The median of physical activity was 85.0 (0–180) minutes/week, and 95 patients (39.9%) reported being sedentary (not any kind of physical activity was performed).

The acceptance rate of the website was 76.06% and according to the type of recruitment, there were statistical differences in age groups, occupation, duration of diabetes, and physical activity. General and socio-demographic characteristics of the study population are reported in Table 1.

Dietary Inflammatory Index

The DII score ranged between − 2.96 (maximal anti-inflammatory diet) and + 7.21 (maximal pro-inflammatory diet) (Fig. 1). The DII score as a dichotomous variable; a higher inflammatory index score was associated significantly (p 0.002) with combined therapy (oral antidiabetic medications and insulin) and a lower education level with a significantly (p 0.047) higher DII score. Age and sex were not significantly different in DII scores. The proportion of participants with low physical activity was also observed progressively and increasingly in higher values of DII score, but the difference did not reach statistical significance. Values and socio-demographic characteristics of DII score are shown in Supplementary information (Appendix A. Supplementary data, Table 2).

Tests applied on study population

Profile of psychological stress

The assessment of stress variables, 79 participants (33.2%) obtained a score that indicated stress perceived; 137 patients (57.6%) presented psychological stress; and 146 patients (61.3%) presented EB from the subscale. There were no significant differences between groups (Appendix A. Supplementary data, Table 3).

Regarding dichotomous DII, psychological stress and EB, PD, and RD subscales showed significant differences across values of DII. Mainly, the participants with stress exhibited pro-inflammatory values (67.9%) and with EB subscale (68.5%), with significant differences across DII scores ($p < 0.05$) (Appendix A. Supplementary data, Table 4).

Assessing self-management and quality of life

We evaluated self-management, and we found effective glucose management by 158 (66.4%) participants; no significant differences were observed between groups. Medical treatment adherence was reported by 56 (23.5%) patients. Only 39 participants (16.5%) obtained a favorable lifestyle category. In the lifestyle domains, the proportion of persons with a favorable score of effort to eat well, and cooking capacity were significantly lower in the high values of DII score ($p < 0.05$) (Appendix A. Supplementary data, Table 4).

We analyzed the relationship between psychological stress and barriers to diabetes self-management, demonstrating a relation between domains of DSS and adherence (p 0.007) and cooking capacity (p 0.004). Based on correlation analysis, significant positive associations between DII and E-DII ($r = 0.68$), adherence and lifestyle ($r = 0.36$), effort to eat well and lifestyle ($r = 0.28$), and adherence and effort to eat well ($r = 0.49$) were found. Negative associations were identified in DII scores and adherence ($r = -0.20$), lifestyle ($r = -0.11$), cooking capacity ($r = -0.26$), and effort to eat well ($r = -0.23$), in which adherence and effort to eat well were the most highly correlated ($r = 0.49$, $p < 0.0001$) (Fig. 2).

Models of logistic regression

After adjusting for age and sex, DII as a continuous or categorical variable, correlation between psychological stress and DII was significant; results are presented in Table 2. DII as a continuous variable showed a per-point decrease as a role of a protective factor of psychological stress in T2D (OR 0.86, 95% CI 0.74, 0.98; p 0.033). Compared with the participants that obtained lower scores, those in the upper scores of DII had 2.40 times (95% CI 1.2, 4.6; p 0.010, $r^2 = 0.113$) higher odds of having psychological stress after adjustment for potential confounders (Table 2, Fig. 3). Similarly, participants with higher scores of DII had 2.49 times (95% CI: 1.2, 4.9; p 0.009, $r^2 = 0.110$) higher odds of having emotional distress in comparison to subjects with the lowest DII scores (Appendix A. Supplementary data, Table 7).

Table 1 Characteristics of the study population with type 2 diabetes

	Overall study ($n=238$)	Community-based approach ($n=37$)	Diabetes clinic ($n=201$)	p
Sex, *n* (%)				
Male	100 (42.0)	18 (18.0)	82 (82.0)	0.374
Female	138 (58.0)	19 (13.8)	119 (86.2)	
Age, *y* *	55.54 ± 12.10	47.68 ± 9.49	56.99 ± 11.99	0.0001
Age groups, *n* (%)				
< 45	47 (19.7)	15 (31.9)	32 (68.1)	0.0001
45–60	101 (42.4)	18 (17.8)	83 (82.2)	
> 60	90 (37.8)	4 (4.4)	86 (95.6)	
BMI, kg/m^2 *	28.59 ± 5.57	29.95 ± 6.05	28.34 ± 5.45	0.139
Weight status, *n* (%)				
BMI < 24 kg/m^2	49 (20.6)	2 (4.1)	47 (95.9)	0.041
BMI 24–28 kg/m^2	71 (29.8)	12 (16.9)	59 (83.1)	
BMI > 28 kg/m^2	118 (49.6)	23 (19.5)	95 (80.5)	
Occupation, *n* (%)				
Unemployed	21 (8.8)	0 (0.0)	21 (100)	0.0001
Housekeeper	116 (48.7)	11 (9.5)	105 (90.5)	
Pensioner	8 (3.4)	4 (50.0)	4 (50.0)	
Active worker	93 (39.1)	22 (23.7)	71 (76.3)	
Educational level, *n* (%)				
None	21 (8.8)	1 (4.8)	20 (95.2)	0.0001
Low	131 (55.0)	9 (6.9)	122 (93.1)	
Medium	42 (17.6)	9 (21.4)	33 (78.6)	
Medium–high	33 (13.9)	9 (27.3)	24 (72.7)	
High	11 (4.6)	9 (81.8)	2 (18.2)	
Medications, *n* (%)				0.351
Oral antidiabetic medications	81 (34.4)	16 (19.8)	65 (80.2)	
Insulin therapy	27 (27.5)	3 (11.1)	24 (88.8)	
Mix	130 (38.1)	18 (13.8)	112 (86.2)	
Duration of diabetes, *n* (%)				
< 10 y	119 (50.0)	27 (22.7)	92 (77.3)	0.002
≥ 10 y	119 (50.0)	10 (8.4)	109 (91.6)	
Smoking, *n* (%)				
Never-occasionally	205 (86.1)	27 (13.2)	178 (86.8)	0.012
Usually	33 (13.9)	10 (30.3)	23 (69.7)	
Alcohol status, *n* (%)				
Never-occasionally	209 (87.0)	31 (14.8)	178 (85.2)	0.415
Usually	29 (12.2)	6 (20.7)	23 (79.3)	
Physical activity duration, *n* (%)				
MET- m/w*	306.4 ± 23.8	378.0 ± 62.5	293.3 ± 25.6	0.522
< 150 m/w	163 (68.5)	20 (12.3)	143 (87.7)	0.040
≥ 150 m/w	75 (31.5)	17 (22.7)	58 (77.3)	
DII score (−9 to +8) *	2.38 ± 2.04	2.65 ± 1.83	2.33 ± 2.08	0.469
E-DII score (−5.81 to 4.82) *	2.82 ± 1.11	3.37 ± 0.79	2.72 ± 1.14	0.469
Effective glucose management, *n* (%)	158 (66.4)	24 (15.2)	134 (84.8)	0.769

Description of characteristics of the study population are presented by type of recruitment and general. Educational levels were considered without completion of any education system, elementary–middle school, high school, bachelor, and postgraduate degrees. A mix of antidiabetic medications was included: oral medication and insulin therapy. Consumption of alcohol and smoking were categorized by amounts and frequency. p Value < 0.05. *Values are presented as mean ± SD. Abbreviations: *DII* Dietary Inflammatory Index, *E-DII* Energy–Density Dietary Inflammatory Index, *n* number, *m/w* minutes per week, *y* year

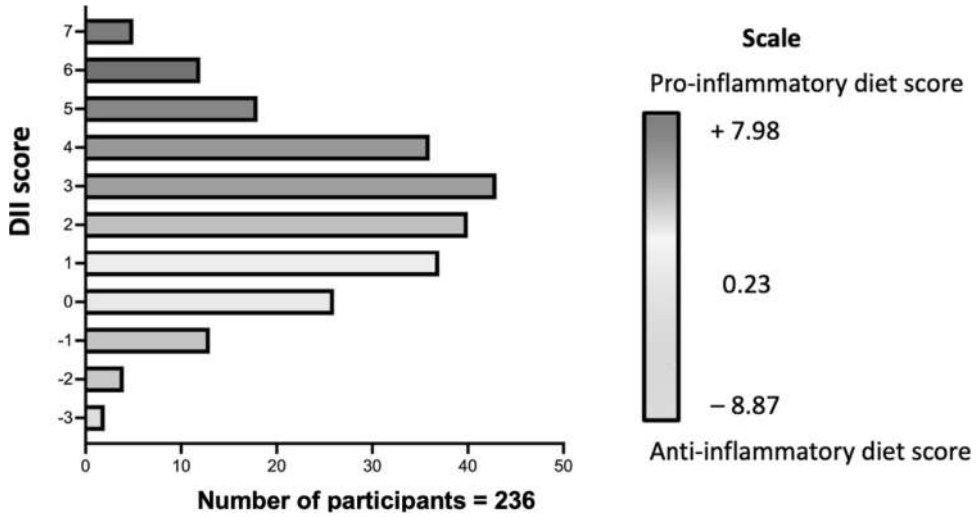

Fig. 1 DII scores obtained from the study population. Frequency distribution of DII is presented. A summary of the frequency distribution by DII individual score shows a concentration of participants in the zone of a pro-inflammatory score. The scale contained global scores as the reference of the global database. The red color is indicative of the highest profile of inflammation (maximal pro-inflammatory diet up to + 7.98), and the green color is indicative of the highest profile of anti-inflammation (maximal anti-inflammatory DII score up to − 8.87). Middle colors are orientated to a neutral transition (median is + 0.23). *Y*-axis: individual DII scores obtained in our population. *X*-axis: number of participants. Abbreviations: DII, Dietary Inflammatory Index

Sensitivity analysis: comparison with the Energy–Density Dietary Inflammatory Index

A sensitivity analysis was conducted. Thus, correlation analysis was performed, revealing a strong relationship between DII and E-DII ($r = 0.68$, $p < 0.0001$). The highest was the negative correlation between E-DII and effort to eat well ($r = -0.35$, $p < 0.0001$).

Results of the stratified analysis of the subscale of EB and E-DII are shown in Fig. 4. We found that physical activity level acts as a protective factor (OR 0.37, 95% CI 0.20, 0.64; *P 0.001*), and we observed that participants ($n = 46$) with a most pro-inflammatory diet (Q3) had higher odds of having emotional distress in comparison with a most anti-inflammatory diet (Q1) (OR 3.26, 95% CI 1.26, 8.38; *p* 0.014).

Discussion

Our study showed that psychological stress is associated with the consumption of a pro-inflammatory diet in patients with T2D (Table 2, Fig. 3). Most of the patients in our study presented values concentrated in worse scores of a dietary profile of inflammation (Fig. 1) and the presence of psychological stress (Table 3, S2).

We observed that participants with the most-proinflammatory scores had higher OR and showed about twofold higher likelihood of having psychological stress (OR 2.40, 95% CI 1.2, 4.6), compared to participants that consumed a habitual diet with low scores of DII after adjustment for potential confounders, and sensitivity analysis confirmed this association using adjustment by energy. The clinical relevance was 11% ($r^2 = 0.113$), and when DII scores decreased to better values (most anti-inflammatory diet), there is a 14% (2% to 26%) less possibility of having psychological stress (OR 0.86, 95% CI 0.74, 0.98).

Several studies have confirmed that the consumption of pro-inflammatory diets had a higher risk of developing T2D compared with the consumption of anti-inflammatory diets [32, 33]. In this study, the mean DII score in our population was 2.38 and was higher than in other studies, contrary to the mean value of DII in the Mexico City Diabetes Mellitus Survey, which included 27 food parameters with a mean of 0.68 [34], and the Xinjiang population with a mean of 0.81 [35]. However, the National Health and Nutrition Survey ("ENSANUT") reported that one of every two adults in Mexico does not consume fruits and vegetables daily; on the other hand, among the food groups not recommended for daily consumption, the most consumed in Mexican adults were sweetened drinks (69.3%), followed by sweet cereals (41.3%) and sweet snacks and desserts (26.6%) [36]. A more plausible explanation is that our results might suggest that the population consumed more amounts of pro-inflammatory items and nutrients, and less of anti-inflammatory compounds (i.e., polyphenols).

Some studies have proven that a high inflammatory score is also a potent marker of inadequate quality of the diet and may further contribute to chronic stress, which also creates a chain of behaviors that can negatively affect

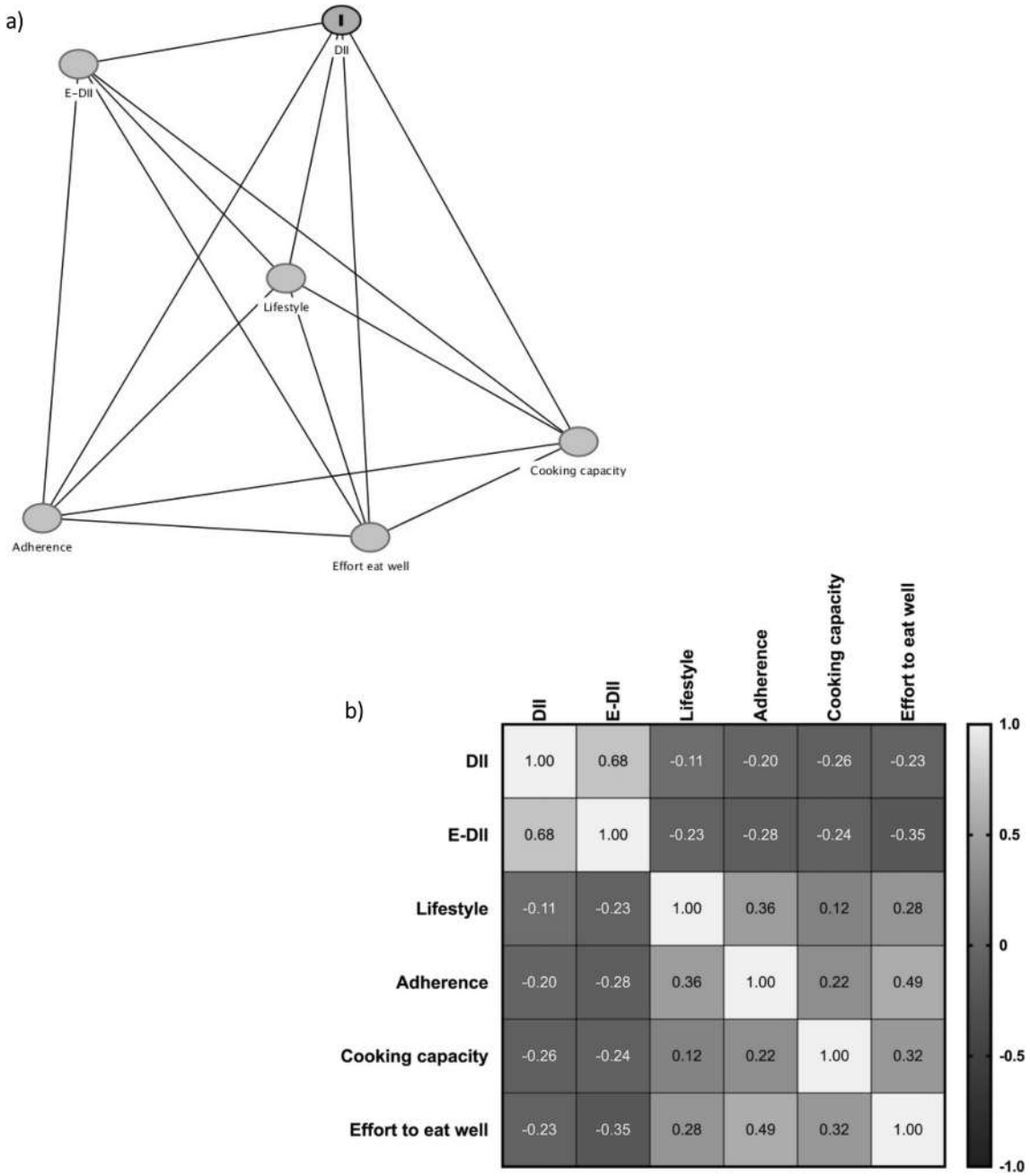

Fig. 2 Correlations between DII, E-II, and total scores from tests applied on study population; lifestyle domains are associated with the DII. **a** DAG scheme of correlations between DII and total scores of different domains of lifestyle assessed through scales obtained from tools applied on study population. **b** Heat map shows the factors associated positively and negatively correlated with DII. Abbreviations: *DAG* directed acyclic graph, *DII* Dietary Inflammatory Index, *E-DII* Energy–Density Dietary Inflammatory Index, *I* outcome

eating habits [32, 37]. In the present study, we evaluated lifestyle domains, showing a negative correlation between DII scores and effort to eat well, in the same way, DII scores and cooking capacity (Fig. 2). Furthermore, we evaluated the presence of EB, and we observed that 57.6% of participants had a have moderate-high emotional distress, of which 68.49% consumed a pro-inflammatory diet (Table 4). Evidence has shown that stress may affect eating behavior, such as emotional eating, lack of time, or motivation to prepare nutritious and balanced meals [38].

Additionally, according to the type of recruitment, statistical differences were observed in the duration of diabetes and physical activity; most of the participants from the diabetes clinic (78.3%) obtained high values of dietary inflammation and combined therapy of oral antidiabetic drugs and insulin. We hypothesize that these differences

Table 2 Results of multivariate logistic regression models examining the relation between the Dietary Inflammatory Index and psychological stress in type 2 diabetes

DII	T2D *n*	Unadjusted OR (95% CI)	*p*	Age and sex-adjusted OR (95% CI)	*p*	Fully adjusted OR (95% CI)	*p*
Continuous variable	236	0.90 (0.79–1.02)	0.123	0.86 (0.75–0.99)	0.038*	0.86 (0.74–0.98)	0.033*
Categorical variable							
D1	61	1 (reference)		1 (reference)		1 (reference)	
D2	175	2.28 (1.2–4.3)	0.011*	2.38 (1.2–4.5)	0.008*	2.40 (1.2–4.6)	0.010* $\mathbf{r^2 = 0.113}$

Simple and multiple logistic regression was performed on the study population with type 2 diabetes. Logistic model fully adjusted: age, sex, PA, BMI, and smoke. DII individual scores as continuous variable is presented. Categorical variable is expressed such as D1 (anti-inflammatory values) versus D2 (pro-inflammatory values). $*p < 0.05$. Abbreviations: *BMI* body mass index, *CI* interval confidence, *n* number, *PA* physical activity, *OR* odds ratio, *T2D* type 2 diabetes

are because people who navigate in the hospital environment have a poor quality of health.

The e-Health tools offer advantages in visual representation and equal instructions in obtained dietary information reducing observer bias in lieu of traditional-based methods [15]. In our study, the data collected on the website suggests that the e-Health approach offered our participants versatility and the possibility of collecting information during the pandemic and creating online innovation elements for a better understanding (e.g., use of images for

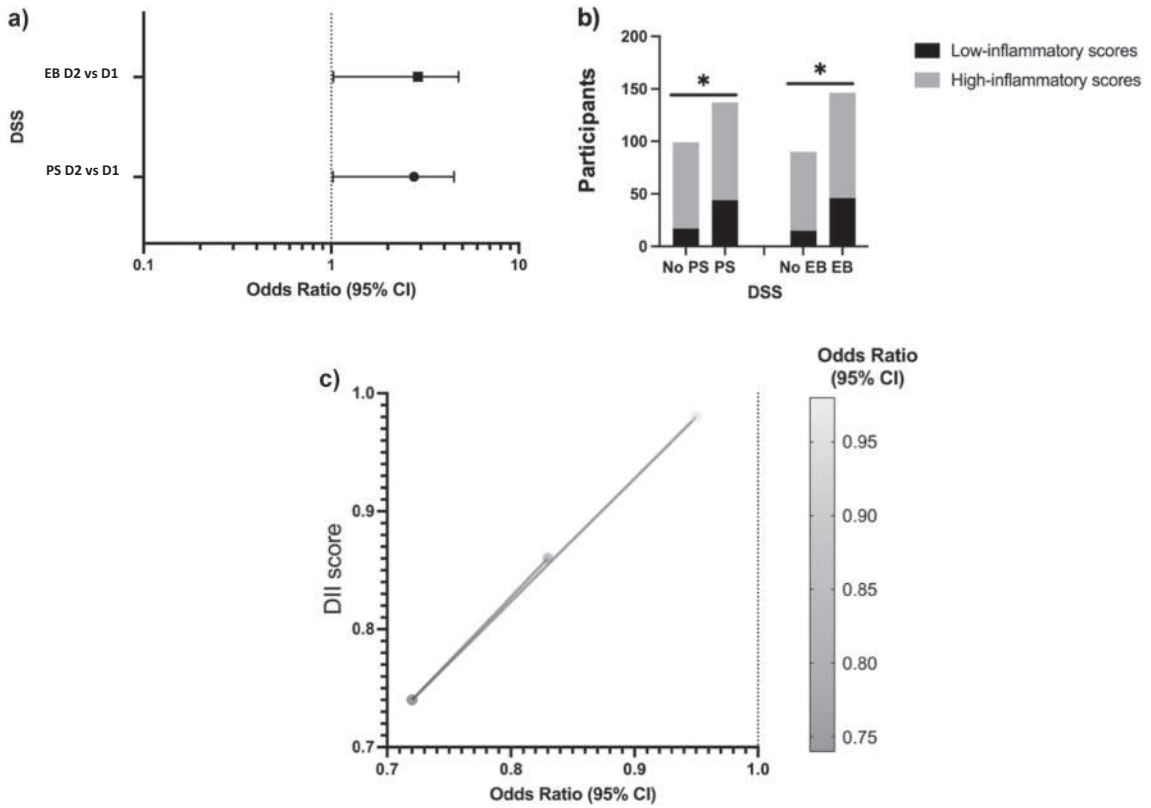

Fig. 3 Odds ratio (95% CI) of DII and DSS. **a** The plot of OR and psychological stress was generated, and an analysis of DII categories (*X-axis*) and values of OR (*Y*-axis) was presented. **b** The plot of OR and EB was generated, and an analysis of DII categories (X-axis) and values of OR (*Y*-axis) was presented. **c** Plotting of the OR of the DSS and EB in relation to DII individuals scores as continues variable is presented. *Y*-axis indicates individual scores of DII obtained of our population. *X*-axis indicates OR values obtained in multiple logistic regression. Blue color indicates final point value of EB and yellow color the final point value of stress. Abbreviations: *CI* confidence interval, *DII* Dietary Inflammation Index, *DSS* Diabetes distress scale, *EB* Emotional Burden distress, *OR* odds ratio, *PS* psychological stress, *vs* versus

portion size estimation); furthermore, we only had an 0.8% drop-out of participants that did not complete the tests and a moderate rate of acceptability to the website; we think that information obtained in web-based tools could reduce costs and time vs traditional methods and improve self-management, offering an alternative to assessment of dietary information.

Previous studies reported increased feasibility of dietary assessment [10, 11], however, in our study, due to the lack of assessment for accuracy on web-based tools, our results cannot confirm feasibility and adoption of e-Health; despite this, we are convinced that it is useful as an emergent technology implying development and progress.

Our methodological barriers were for adequately assessing dietary information which is an actual challenge in nutrition research, and the best methods for dietary collection are still unclear [39]. We noticed that obtaining dietary information on self-report carries the risk of misreporting, which could affect our results. Additionally, we know that seasonality or temporality can affect the collection of dietary information [17]; in our study, this could be modified by nutrient intake or the kind of foods and meals consumed; seasonal variation is beyond the scope of this study's assessment of consumption.

Finally, our population has mostly dietary pro-inflammation values and high BMI levels (overweight and obesity). Studies, in consequence, could be applied to multicenter locations and increased size population of T2D to explore an equilibrium of study population. Conducting studies on cohorts with lower BMI levels in comparison may lead to the discovery of more insightful correlations.

In summary, we demonstrated that there is a significant association between a profile of stress and high inflammatory values of the DII score and relationships with an unfavorable lifestyle and worse DII scores. The low values of the DII score and physical activity may play a protective role against the presence of a profile of stress. Domains of favorable lifestyle in patients with T2D were negatively correlated with individual DII scores. Stress was presented in most of the participants. The analysis presented supports our theory that a pro-inflammatory diet contributes to chronic stress; these results should be confirmed in patients with T2D in further prospective cohort studies, and future clinical trials should consider implementing and establishing strategies for nutritional therapy and anti-inflammatory patterns that might bring light to the dietary treatment of T2D.

People living with T2D in Mexico are characterized by lower consumption of anti-inflammatory and higher consumption of pro-inflammatory compounds; our study revealed that our Mexican population with T2D has scores of dietary inflammation indicative of a pro-inflammatory diet. T2D is a disease with inflammatory activity and per se causes psychological and emotional distress in persons who suffer it. The study's clinical implications highlight the possible potential for preventing diabetes distress by evaluating the inflammatory profile and making adjustments to the consumption of pro-inflammatory compounds while promoting the intake of anti-inflammatory compounds. Anticipating solutions is necessary to innovate new strategies for nutrition therapy focusing on potential inflammatory characteristics of the diet, continuing to assess the most adequate food consumption instrument applied in adults, and promoting healthy environments is required.

Conclusion

We conclude that the use of e-Health through web-based tools to collect information on a website showed a medium rate of acceptability and offered benefits in the application as a method of dietary assessment**,** which requires more studies evaluating accuracy and feasibility. DII and E-DII scores qualify and labeled habitual diet in pro and anti-inflammatory terms and are associated with psychological stress in T2D.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13410-023-01275-4.

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Author contribution All authors read and approved the final manuscript. All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by AISR and RVR. The first draft of the manuscript was written by AISR, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data Availability Data are available upon request from the Corresponding Author.

Declarations

Ethical clearance All participants included in the study gave written informed consent for inclusion. The study was carried out following the Guidelines of the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of *Universidad Autónoma del Estado de México* (register number: 4851/2019E).

Conflict of interest The authors declare no competing interests.

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ORIGINAL ARTICLE

Multivariable prediction model of complications derived from diabetes mellitus using machine learning on scarce highly unbalanced data

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Abstract

Background Diabetes mellitus (DM) increases the risk complications in addition to mortality. Quantifying the risk of complications using artificial intelligence could be a way to design comprehensive patient healthcare programs.

Objective Predicting the probability of macro and microvascular complications in patients with DM through Machine Learning

Methods Retrospective cohort study. Based on an outpatient follow-up program for diabetic patients, 64,081 records and 287 variables were identified, with highly unbalanced data. Predictive models for chronic kidney disease (CKD), lower extremity amputation (LEA), coronary heart disease (CHD), and early mortality (MOR) were developed. An exhaustive computational method was conducted to find the best combination between machine learning (ML) algorithms and sampling method.

Results The best model was determined by assessing its performance through the heuristics obtained from a comprehensive analysis of the accuracy and F1 values for ML, sampling, and dataset. Regarding each complication, 99.9% accuracy was obtained for LEA, 94.3% for CHD, 97.4% for MOR, and 98.8% for CKD. F1 was assessed to identify false positives, with 84.5% for CKD, 63.6% for MOR, 46.2% for LEA, and 44.8% for CHD.

Conclusions This ML model can be applied to predict CHD, CKD, and MOR. The success of ML predictions lies in the clinical definition of initial variables and their simplification for obtaining variables based on which the algorithms can identify patients that are likely to develop a complication. For clinical application of this system, it is necessary to assess the cross performance of metrics, as found here (accuracy higher 95% and F1-Score higher than 80%).

Keywords Complications · Diabetes mellitus · Machine learning · Predictive analytics · Risk predictions

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Introduction

Diabetes mellitus (DM) is a carbohydrate metabolism disorder with high medical costs owing to its associated therapeutic implications, labor disability, acute and chronic complications, and early mortality. Poorly controlled DM increases the incidence of long-term complications, such as retinopathy, kidney disease, peripheral neuropathy, coronary heart disease (CHD), and peripheral vascular disease, all of which have a negative impact on patients, their families, and the society [1]. Around 12% of medical expenses worldwide are associated with treatment of patients with DM and associated complications [2]. Additionally, it has been reported that 366 million people will have DM by 2030, making complication predictions of this disease essential for preventing its health consequences [3, 4].

Statistical models have traditionally been developed for estimating the probability of macro (CHD and peripheral vascular disease) and microvascular complications (retinopathy, kidney disease, and peripheral neuropathy) mainly in populations other than Hispanics living in high-income countries. Thus, in a Japanese population, 5-year predictive models showed high performance for CHD, mortality, and kidney disease (C-statistic of 0.725, 0.696, and 0.767, respectively), but a moderate performance for stroke and retinopathy evolution (C-statistic of 0.636 and 0.614, respectively) [5, 6]. These predictive models have not been validated for Latin American populations nor developed based on real-world data.

The application of machine learning (ML) and data mining to DM research is an imperative and innovative approach, as it enables optimal analysis of large volumes of available data, especially data collected during standard clinical care on patients (diagnosis, tests, samples, biomedical data, etc.) for gathering knowledge and support clinical treatment decision aimed at decreasing the possibility of future complications [7–9]. The MOSAIC project used this strategy to input data (random forest — RF) and balance working bases support vector machine (SVM) for obtaining a 3-, 5-, and 7-year prediction of retinopathy, kidney disease, and peripheral neuropathy disease development through logistic regression [10].

This article aims to generate knowledge based on biological data of patients with DM for predicting the probability of macro and microvascular complications through ML, a complementary tool capable of providing physicians with objective and timely information so that they can treat patients with DM according to their necessities and, eventually, improve the quality of life of patients, their families, and the society.

Materials and methods

Study Design

From an epidemiological perspective, this study employed a retrospective cohort design using data collected from patients enrolled in the "Chronic Diseases Healthcare Program" managed by a Colombian private health insurance company over a 5-year period between 2013 and 2018. All patients who have confirmed DM diagnosis and were admitted to the program in 2013 were included in this study and were followed up to 2018 in order to identify outcomes of interest.

Data sources

Data sources included were Electronic Health Records (Diabetes Registry and Ambulatory Consultation records), Business Intelligence–BI (Drugs and Procedures) systems, and high-cost disease (known as *Cuenta de Alto Costo*) registry issued to national health ministry annually.

Outcomes

Outcomes of interest were chronic complications in patients with DM, specifically:

- Lower extremity amputation (LEA) was defined as any surgical proceedings performed to amputate an extremity in patients with a history of peripheral artery disease, nerve disease, or diabetic foot ulcer
- Chronic kidney disease (CKD) was defined as the presence of albuminuria, low glomerular filtration, or other signs of kidney damage according to the KDIGO guidelines [11].
- Coronary heart disease (CHD), defined as a history of CHD as per clinical records (ICD-10) or surgical proceedings (coronary bypass or stent placement due to coronary artery blockage)
- Mortality (MOR), defined as any cause specified in the death certificates

Predictors

A literature review was performed in order to identify the ideal set of variables (predictors) for each model. In general, predictors considered were data related to sociodemographic (sex, age, date of admission to the program, and city of residence), clinical (tobacco use, medical and surgical history, physical examination data, and prescription and/or use of antihypertensive drugs, NSAIDs, oral hypoglycemic drugs, and/or insulin), and laboratory (levels of glycemia, creatinine, albumin, albuminuria, creatinuria, lipids, hemoglobin, glycosylated hemoglobin (HbA1c), glomerular filtration rate (GFR), parathormone, and phosphorus) information. Minimal and ideal set of predictors for each model (LEA, CKD, CHD, MOR) is presented in Supplementary Information (Table S1). These predictors were derived from the literature review and were deemed most appropriate for each specific model.

Sample size

All patients from a private healthcare insurer network that met the eligibility criteria during 2013 and 2018 and had updated information were included.

Machine learning

For ML analysis, an incremental iterative method was applied, which was adapted based on the guidelines for predictive data mining in clinical medicine, derived from

CRISP Data Mining Methodology Extension for Medical Domain [12], and was structured into four steps: data preparation, data preprocessing, training, and validation (Supplementary information, Fig. S1).

Data preparation

Original records were organized in a semi-structured manner (Supplementary information, Table S2), and there was a wide heterogeneity among patients. For each patient, variables of interest were reported annually, ranging from unreported (no data) to up to 20 annual reports per patient, with an irregular time pattern. Included variables were selected based on scientific evidence and/or medical literature showing a correlation between the reports and the predicted complication.

Condensation of repeated-measure variables was used to consolidate multiple data collection procedures, such as blood pressure or laboratory data (Cholesterol or HbA1c), into one. For doing this, two summarization methods were applied: absolute variation of repeated measures (AVRM) and coefficient of variation (CV) calculation. Data imputation was developed by estimating the average value in a group of patients using the K-Means (Supplementary information, Fig. S2) technique and dividing the data into *n* clusters of equal variances. The value to be imputed was determined as the average of a subgroup, minimizing inertia or the sum of squares within the cluster. The Elbow method was used to determine the number of clusters to be used (Supplementary information, Fig. S3).

Pre-processing and predictor selection

For addressing this highly unbalanced data, different imputation sampling techniques were applied (over and undersampling) and complemented by a random selection of patients without complications to generate three additional datasets called "random 30–45–60%" from which 30%, 45%, or 60% of patients were randomly removed and mixed with patients that did develop a complication (Fig. 1).

After the values were summarized and imputed, variables with the highest influence over each type of complication were determined. Variables that did not contribute to the predictive process were eliminated through correlation analysis (Supplementary information, Fig. S5) Sequential forward floating selection technique (SFFS) in conjunction with a cross-validation scheme validated ML performance, based on K-Fold. Feature extraction is based on sequential engineering based on different techniques such as univariate analysis using chi-square, tree-like classifiers, and progressive sequencing with selection techniques.

Training

Overall, as shown in Fig. 1, training was performed for each complication, with eight datasets (ALL, ALL imputed, and sampling 30%, 45%, and 60% imputed or not imputed), ten sampling methods: random oversampling (ROS); SMOTE; BorderLine SMOTE; BLSMOTE); SVM SMOTE (SVMSMOTE); ADASYN (ADASYN); Tomek Links (TL); edited nearest neighbors (ENN); repeated edited nearest neighbors (RENN); neighborhood cleaning rule (NCR); SMOTE and edited nearest neighbors (SMENN): combine under and oversampling), and ten ML algorithms: multinomial logistic regression (LR); linear discriminant analysis (LDA); decision tree (CART) (classification and regression tree); support vector machine (SVM); k-nearest neighbors (KNN); Bagged Decision Trees (BAG); random forest (RF); extra trees (ET); Gaussian process classifier (GPC); Gaussian naive Bayes (GNB), which resulted in a total of 3200

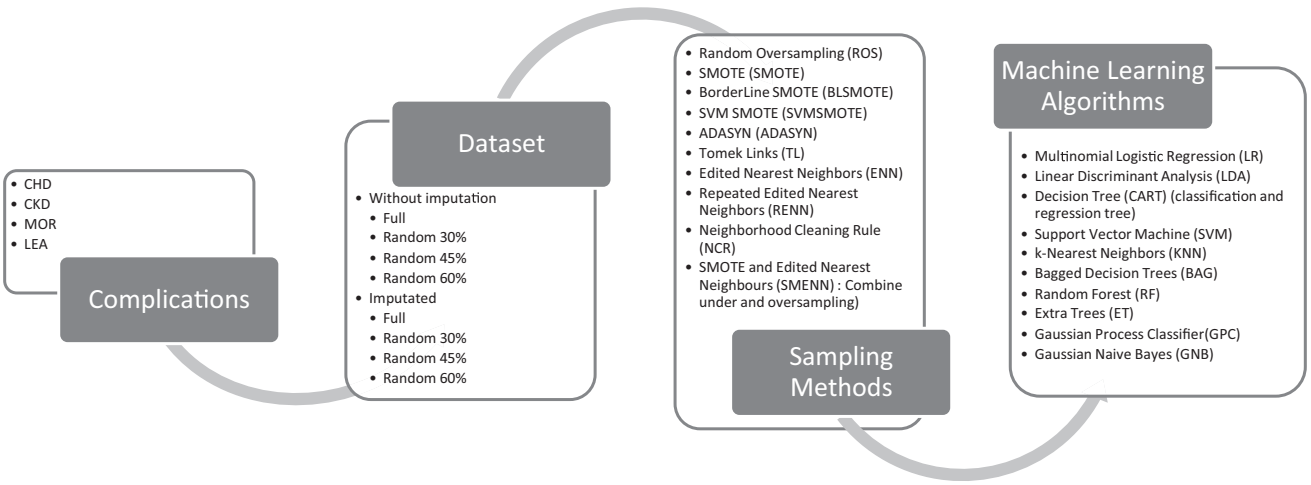

Fig. 1 General process followed to obtain relevant ML for predicting CHD, CKD, MOR, and LEA

trainings to be conducted with *each initial set of variables and patients*. Using this approach, it is possible to comprehensively review the behavior of a group of variables and avoid the elimination of sampling methods (over and undersampling), certain ML algorithms, or bias induced by statistical engineering of characteristics [13]. Blind assessment was omitted due to the novelty method to perform mathematical evaluation of the ML models outcome. This is a key factor to include in a long-term study, where an individual and detailed clinical follow-up will be performed, to evaluate if the ML model predicts a real case or false positive.

Validation

For addressing highly unbalanced data, over and undersampling were applied and supplemented by a random selection of patients with no complication. Moreover, to validate the performance of each model and its capacity for responding to new data or a generalization, the sample of each possible dataset was divided into 80% for training and 20% for testing (Fig. 2). The generalizing capacity of the models was validated using an error matrix.

An exhaustive, combinatorial algorithmic processing was performed to determine the combination (ML-sampling-biomarkers) with the best performance. Mass training was performed with different combinations of variables and processing techniques per patient group instead of choosing a given algorithm.

Accuracy was used to determine the models' general performance, which was supplemented by a recall analysis for identifying cases in which the algorithm successfully predicts a complication and a precision analysis for determining cases in which the algorithm does not predict a complication and the complication does occur. The aim was to find the best performance for predicting complications, especially for avoiding false negatives by assessing the F1-Score value as a harmonic mean of precision (specificity) and recall (sensitivity) values. A heuristic validation (HV) was chosen based on accuracy heuristics and F1 heuristics, which were obtained by a sigmoid function applied to each metric as a correction factor over the performance of three datasets (training, test, and cross-validation).

Ethics considerations

This study was reviewed and approvals obtained to use the data for analysis by the Ethics Committee of the Fundación Universitaria Sanitas (CEIFUS 320–18). The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Results

Participants and predictors

The initial dataset included 64,081 patients and 287 variables, which was restricted to patients with at least a year of follow-up between 2013 and 2018, resulting in a total of 28,828 patients (Supplementary information, Fig. S2). The 287 variables were reduced to 21 by applying a systematic grouping process over time defined in the preprocessing stage (Table 1; Fig. 3). The final set of variables included sex, age, socioeconomic status, body mass index (BMI), mean blood pressure, glycemia, HbA1c, total cholesterol, HDL cholesterol, LDL cholesterol, hemoglobin, GFR, CKD stage (KDIGO classification), kidney transplant history, hypertension, ACE inhibitor or ARB-2 prescription, insulin

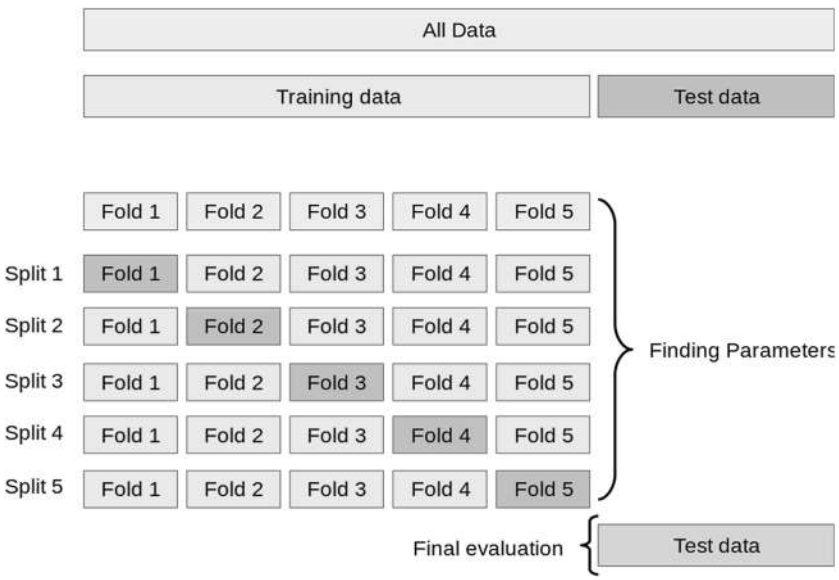

Fig. 2 Cross-validation scheme for validating ML performance, based on K-fold

Table 1 Features names selection for each outcome

Outcome	Summarize shape of dataset	Target prediction VaR distribution	Feature names or variables per VaR amount
Heart Disease/CHD	101,960, 25	Class = 0, count = 61,333, percentage = 60.154% Class = 1, count = 40,627, percentage = 39.846%	13: gender, age, SBP, Hba1c, cholesterol HDL, hemoglobin, GFR, IECA, ARB-2, socioeconomic status, hypertension, insulin, metformin 12: gender, age, SBP, Hba1c, cholesterol HDL, hemoglobin, GFR, IECA, ARB-2, socioeconomic status, hypertension, insulin, metformin 11: gender, age, SBP, Hba1c, cholesterol HDL, hemoglobin, GFR, IECA, ARB-2, socioeconomic status, hypertension, insulin, metformin 15: gender, age, SBP, DBP, total cholesterol, cholesterol HDL, hemoglobin, GFR, history of kidney transplantation, IECA, ARB-2, socioeconomic status, hypertension, insulin, metformin 16: gender, age, SBP, DBP, Hba1c, total cholesterol, cholesterol HDL, hemoglobin, GFR, history of kidney transplantation, IECA, ARB-2, socioeconomic status, hypertension, insulin, metformin
Chronic kidney disease	64,081, 25	Class = 0, count = 63,029, percentage = 98.358% Class = 1, count = 1052, percentage = 1.642% Distribution of class labels BEFORE resampling counter ({0: 63,029, 1: 1052}) Distribution of class labels AFTER resampling counter ({0: 63,029, 1: 63,029})	15: gender, age, SBP, DBP, total cholesterol, cholesterol HDL, hemoglobin, GFR, history of kidney transplantation, IECA, ARB-2, socioeconomic status, hypertension, insulin, metformin 16: gender, age, SBP, DBP, Hba1c, total cholesterol, cholesterol HDL, hemoglobin, GFR, history of kidney transplantation, IECA, ARB-2, socioeconomic status, hypertension, insulin, metformin 14: gender, age, SBP, DBP, total cholesterol, cholesterol HDL, hemoglobin, GFR, history of kidney transplantation, IECA, ARB-2, socioeconomic status, hypertension, insulin 13: gender, age, SBP, DBP, total cholesterol, hemoglobin, GFR, history of kidney transplantation, IECA, ARB-2, socioeconomic status, hypertension, insulin
Lower extremity amputation	64,081, 25	Class = 0, count = 62,780, percentage = 97.970% Class = 1, count = 1301, percentage = 2.030% Distribution of class labels BEFORE resampling counter ({0: 62,780, 1: 1301}) Distribution of class labels AFTER resampling counter ({0: 62,780, 1: 62,780})	14: age, kidney disease progression, glycemia, creatinine, HbA1C, total cholesterol, cholesterol LDL, hemoglobin, GFR, history of kidney transplantation, hypertension, insulin, metformin 13: age, kidney disease progression, glycemia, creatinine, HbA1C, total cholesterol, cholesterol LDL, hemoglobin, GFR, history of kidney transplantation, hypertension, insulin, metformin 12: age, kidney disease progression, creatinine, HbA1c, total cholesterol, cholesterol LDL, hemoglobin, GFR, history of kidney transplantation, hypertension, Insulin, metformin 11: age, kidney disease progression, creatinine, total cholesterol, cholesterol LDL, hemoglobin, GFR, history of kidney transplantation, hypertension, insulin, metformin 10: age, kidney disease progression, creatinine, cholesterol LDL, hemoglobin, GFR, history of kidney transplantation, hypertension, Insulin, metformin

Table 1 (continued)

Outcome	Summarize shape of dataset	Target prediction VaR distribution	Feature names or variables per VaR amount
Mortality	64,081, 25	Class = 0, count = 63,975, percentage = 99.835% Class = 1, count = 106, percentage = 0.165% Distribution of class labels BEFORE resampling counter ({0: 63,975, 1: 106}) Distribution of class labels AFTER resampling counter ({0: 63,975, 1: 63,975})	23: gender, age, BMI, kidney disease progression, SBP, DBP, glycemia, creatinine, Hba1c, total cholesterol, cholesterol HDL, hemoglobin, GFR, history of kidney transplantation, hypertension, IECA, ARB-2, CKD, insulin, metformin, DPP4 inhibitors 20: gender, age, BMI, kidney disease progression, SBP, DBP, glycemia, creatinine, Hba1c, total cholesterol, cholesterol HDL, cholesterol LDL, hemoglobin, GFR, history of kidney transplantation, hypertension, CKD, insulin, metformin 21: gender, age, BMI, kidney disease progression, SBP, DBP, glycemia, creatinine, Hba1c, total cholesteroL, cholesterol HDL, cholesterol LDL, hemoglobin, GFR, history of kidney transplantation, hypertension, CKD, socioeconomic status, insulin, metformin 22: gender, age, BMI, kidney disease progression, SBP, DBP, glycemia, creatinine, Hba1c, total cholesterol, cholesterol HDL, cholesterol LDL, hemoglobin, GFR, history of kidney transplantation, hypertension, ARB-2, CKD, socioeconomic status, insulin, metformin 24: gender, age, BMI, Kidney disease progression, SBP, DBP, glycemia, creatinine, Hba1c, Total Cholesterol, cholesterol HDL, Cholesterol LDL, hemoglobin, GFR, history of kidney transplantation, hypertension, IECA, ARB-2, CKD, socioeconomic status, insulin, Metformin, DPP4 inhibitors

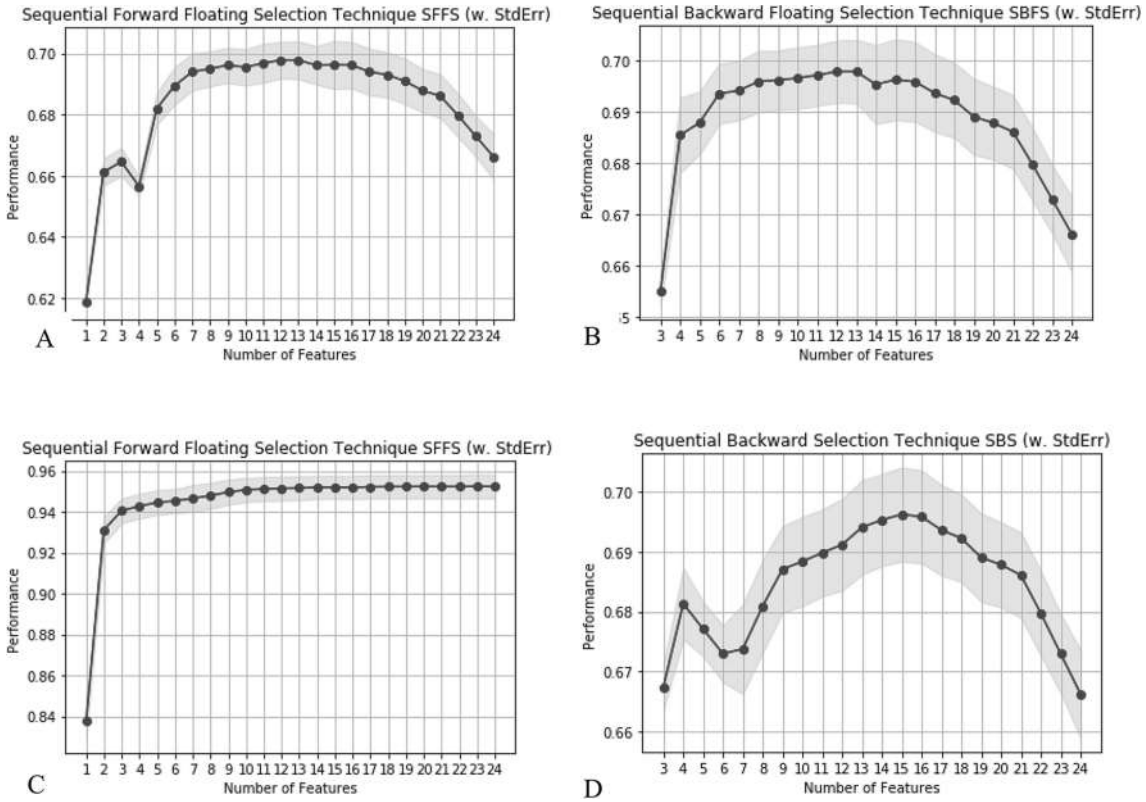

Fig. 3 Sequential forward floating selection technique (SFFS) per complication. **A** Heart Disease/ CHD; **B** Chronic Kidney Disease – CKD; **C** Lower Extremity Amputation – LEA; **D** Mortality - MOR

administration, metformin, and DPP4 inhibitor prescription (Table 2).

Model performance

The performance of dataset with and without imputation is presented for each complication in Supplementary information, Table S3. According to accuracy, there is no significant variation between the datasets (ALL — complete dataset) with missing records and the imputed ones (ACC > 94%). For Precision over class (PRE) measure, the imputed dataset (ALL — complete dataset) presents on average better performance for all outcomes (98.7% vs. 87.1%). If the average of all metrics is taken as a whole, the imputed dataset performs better (69.3% vs. 65.1%). This way of looking at the data is a starting point, but not decisive, since what really matter is to avoid false negatives and false positives.

Once the feasibility of using the selected datasets has been determined, it is necessary to evaluate which ML technique performs best, given the sampling method to be applied. The F1-Score metric is evaluated first, then precision and recall.

For CHD (Supplementary information, Table S4), the best result was obtained with the imputed dataset R30%_IMP, the BAG ML, and ROS sampling; HV was 58.3%, with a weighted accuracy of 77.5% and F1 of 39%. For LEA (Supplementary information, Table S5), the best result was obtained with the non-imputed dataset R30%, the LDA ML, and SVMSMOTE sampling or with no sampling (NONE); HV was 53.5%, with a weighted accuracy of 81.2% and F1 of 25.8%. For CKD (Supplementary information, Table S6), both RF and BAG algorithms yielded the same result; the first one was obtained with BorderLine SMOTE (BLSMOTE) or SVMSMOTE sampling and the second one with ROS sampling, with an imputed dataset R30%_IMP. HV was 71.8%, with a weighted accuracy of 80.8% and F1 of 62.7%. For MOR, RF was observed with ROS (67.2% HV) and SVMSMOTE (66.8% HV) samplings, with an imputed dataset R30%_IMP (Table 3).

The following maximum performance values were obtained per complication with cross heuristic evaluation: 77.5% for CHD, 81.2% for LEA, 80.9% for CKD, and 79.7% for MOR (Fig. 4). In general, accuracy was approximately 80%. The F1-Score Heuristic Validation (F1_ Heu) metric varied significantly per complication, CKD showing the highest performance, followed by MOR. For CHD and LEA, the results obtained were low for a system that is under production.

Table 2 Patients' description according to presence of complications

Variable	All *N* = 28.828 *n* (%)	No complications *n* = 26.077 *n* (%)	LEA *n* = 44 *n* (%)	CHD *n* = 1520 *n* (%)	CKD *n* = 641 *n* (%)	MOR *n* = 773 *n* (%)
Sex						
Male	12,733 (44.2)	11,144 (42.7)	28 (63.6)	918 (60.4)	415 (64.7)	381 (49.3)
Female	16,095 (55.8)	14,933 (57.3)	16 (36.4)	602 (39.6)	226 (35.3)	392 (50.7)
Age[a] (years)	67 (59–74)	66 (58–74)	67 (58–73)	68 (62–73.5)	64 (55–71)	77 (70–83)
Socioeconomic status						
0	2580 (8.9)	2312 (8.9)	5 (11.4)	148 (9.7)	81 (12.6)	64 (8.3)
1	17,797 (61.7)	16,049 (61.5)	23 (52.3)	1.034 (68.0)	361 (56.3)	466 (60.3)
2	1153 (4.0)	1027 (3.9)	3 (6.8)	78 (5.1)	30 (4.7)	29 (3.7)
3	3004 (10.4)	2755 (10.6)	5 (11.4)	103 (6.8)	64 (9.9)	89 (11.5)
4	604 (2.1)	541 (2.1)	2 (4.6)	33 (2.2)	19 (2.9)	16 (2.1)
5	3690 (12.8)	3393 (13.0)	6 (13.6)	124 (8.2)	86 (13.5)	109 (14.1)
History of hypertension	26,006 (90.2)	23,495 (90.1)	38 (86.4)	1426 (93.8)	528 (82.4)	722 (93.4)
ACE inhibitor consumption	7109 (24.7)	6363 (24.4)	15 (34.1)	454 (29.9)	93 (14.5)	229 (29.6)
ARB consumption	14,572 (50.5)	13,038 (50.0)	23 (52.3)	896 (58.9)	328 (51.2)	419 (54.2)
Metformin consumption	22,908 (79.5)	21,064 (80.8)	28 (63.6)	1216 (80.0)	193 (30.1)	490 (63.4)
DPPIV inhibitor consumption	9758 (66.2)	8803 (33.8)	12 (27.3)	586 (38.6)	210 (32.8)	231 (29.8)
Insulin use	9032 (31.3)	7770 (29.8)	33 (75.0)	637 (41.9)	403 (62.9)	350 (45.2)
History of CKD	9655 (33.5)	8257 (31.7)	19 (43.2)	636 (41.8)	-	403 (52.1)
BMI[a]	26.7 (24.1–29.8)	26.8 (24.2–29.9)	24.6 (22.6–26.8)	27.0 (24.5–29.9)	25.3 (22.9–28.4)	24.8 (22.2–27.6)
MBP[a]	91.3 (88.6–94.1)	91.3 (88.7–94.2)	89.3 (87.0–94.2)	90.7 (88.1–93.8)	92.5 (88.9–96.5)	89.4 (86.5–92.9)
Glycemia[a]	121.2 (106.5–144.9)	121.1 (106.5–144.5)	131.1 (104.3–173.7)	123.2 (107.6–147.8)	122.5 (101.0–158.2)	120.3 (105.1–147.0)
HbA1c[a]	6.7 (6.2–7.5)	6.7 (6.2–7.4)	7.0 (6.1–8.3)	6.7 (6.2–7.6)	6.8 (6.0–7.7)	6.8 (6.2–7.6)
Total cholesterol[a]	179.4 (157.1–202.2)	180.5 (158.8–203.0)	174.8 (134.2–206.7)	164.7 (141.3–186.9)	172.0 (145.5–200.9)	170.7 (144.1–195.0)
HDL cholesterol[a]	45.0 (38.1–53.7)	45.2 (38.4–53.9)	44.1 (35.6–60.1)	42.2 (35.9–50.6)	40.4 (34.7–49.4)	46.3 (38.3–54.8)
LDL cholesterol[a]	97.7 (78.9–117.5)	98.7 (80.2–118.4)	83.3 (69.4–115.2)	85.1 (67.3–105.0)	93.1 (71.9–115.2)	90.8 (70.4–111.2)
Hemoglobin[a]	14.4 (13.2–15.5)	14.5 (13.3–15.5)	11.7 (10.3–14.3)	14.0 (12.6–15.2)	11.6 (10.8–12.7)	111.2 (11.4–14.2)
GFR[a]	75.5 (61.2–87.7)	76.6 (63.1–88.5)	67.0 (37.9–87.8)	67.8 (54.3–81.3)	16.2 (8.4–43.8)	59.6 (41.1–74.7)

HT arterial hypertension, *ACE* angiotensin converter enzyme, *ARB* angiotensin II receptor blockers, *DPPIV* dipeptidyl peptidase IV, *CKD* chronic kidney disease, *BMI* body mass index; *MBP* median blood pressure, *HbA1c* glycated hemoglobin, *HDL* high-density lipoproteins, *LDL* low-density lipoproteins, *GFR* glomerular filtration rate

[a]Reported as median and interquartile range

Table 3 Performance consolidated per ML, sampling, and complication

Complication	ML	Sampling	Accuracy	F1-Score	Precision	Recall
AEI	LDA	BLSMOTE	99.9%	46.2%	100.0%	30.0%
ECC	BAG	NONE	94.3%	44.8%	87.0%	33.6%
MOR	RF	ROS	97.4%	63.6%	98.0%	50.9%
ERC	RF	NONE	98.8%	84.5%	94.2%	81.8%

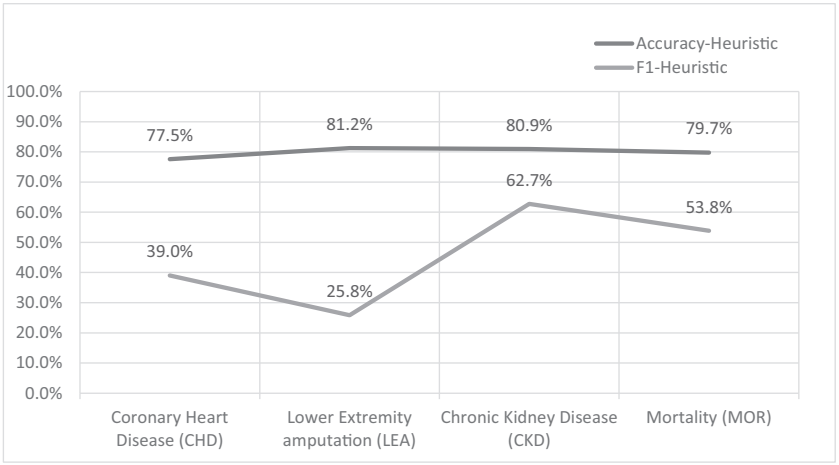

Fig. 4 Performance of the prediction model (ML) for complications associated with diabetes mellitus

Discussion

This paper demonstrates how data mining and computational methods can provide efficient insights for clinical practice through personalized models using individualized and real-time information for each patient for predicting an outcome of interest. Data mining predictive methods can be applied to the development of decision models for procedures like prognosis, diagnosis, and treatment planning. After these have been evaluated and verified, they can be included into automatic and real-time systems of clinical data.

The most relevant variables of our models, according to their potential capacity as early markers for the development of complications, vary per each one of them. The same set of variables was used, but the less predictive were eliminated: For CHD outcome, the correlated variables LDL cholesterol, HDL cholesterol, consumption of ARA2 drugs, GFR, and HbA1c; in the case of chronic kidney disease (CKD), the variables LDL cholesterol, HDL cholesterol, consumption of ACE inhibitors, glycemia, and hemoglobin were eliminated; for lower extremity amputation (LEA), LDL cholesterol, HDL cholesterol, glycemia, and hemoglobin were eliminated; for the mortality (MOR) case, LDL cholesterol, HDL cholesterol, consumption of ACEI drugs, glycemia, and hemoglobin were eliminated.

The best approach to be applied for algorithm assessment needs to be determined. First, a general segmentation of the dataset, comprising imputed and non-imputed data and data applicable to different sampling techniques and ML algorithms, is recommended. This is only possible by performing an exhaustive computational processing, where multiple models are trained based on different sampling techniques and datasets. In this study, more than 3200 experiments were performed, allowing elimination of general hypotheses, such as the one stating that algorithms work better with imputed datasets. For LEA, the best performance was obtained with the non-imputed dataset and without any sampling methods. Based on the tests performed, it could be stated that imputation tends to improve performance (CHD, CKD, and MOR work better); however, this is not a general rule, as in some health predictions (such as LEA), class balancing (patients without complications vs. with complications) and correlation between variables and complications to be predicted are more important.

The algorithm's evaluation depends on its intended use, i.e., it is determined based on the relevance of false positives and false negatives. Accuracy, as a general assessment method, should be revised and used carefully to avoid false negatives. For this reason, the sole evaluation of accuracy is highly limited, and metrics, such as F1-Score, need to be assessed. The F1-Score was the most important metric in this case as the aim was to avoid false negatives or justify the lack of complication when the patient was going to develop it. Based on the obtained results, the CKD case can be used in a clinical environment given its performance in all indicators (80.9% ACC_Heu and 62.7% F1_Heu). For MOR prognosis, its use should be limited to the prognosis of true positives (precision) and interpretation of false positives. For CHD and LEA, its use in clinical environments should be evaluated given its low performance in recall, precision, and F1, even though its performance is close to 80% for accuracy metric heuristic validation (ACC_Heu).

It is noteworthy that by evaluating applicability of the models, the best result was obtained for cases associated with kidney complications. The other models and complications may yield better results if their observation window is broadened, or if the variables are supplemented by unequivocal clinical elements, such as creatinine for CKD. At first, this is particularly interesting because it evidences that an algorithm can help physicians identify patients needing special healthcare by calculating future risk level.

These results are novel as they show alternative options for the treatment of variables, which yield higher metrics in the prediction of CKD (without HV heuristics), such

as 81.2% accuracy, 84.5% F1-Score, 94.2% precision, and 81.8% recall. This is evidenced by comparing the aforementioned metrics with the ones reported by Casanova et al. (75% accuracy, 74% recall, and 75% precision) [14], Rau et al. (75% recall and 87.3% F1) [15], Chen et al. (88.6% accuracy) [16], Huang et al. (65.2% accuracy, 63.2% recall, and 67.2% precision) [17], and Chu Su et al. (87% accuracy, 88% precision, and 83% recall) [18].

The success of ML algorithm predictions lies in correct definition, exploration, and assessment of variables based on which algorithms can effectively distinguish patients who may develop a certain complication. All technical efforts should be focused on improving the models, without overfitting and assessing the metrics directly related to prediction of a future disease or the correct prediction of the class showing a complication. Moreover, it is vital to conduct this type of study with a clinical proposal on the correlation between the variables and the element to be predicted; although statistics is useful, assumptions require scientific validation. Variable management over time is essential, and it has been evidenced that synthesizing variables over time using new methods (VAMR or CV) results in insights or key elements based on which machines can make correct predictions on the risk of a complication. Variables forming a dataset must be imputed, and their result must be validated. An exhaustive computational search on the performance of an algorithm should be performed, using an imputed or non-imputed dataset, in addition to accurate application of sampling methods for predicting a given complication.

Some strengths need to be highlighted. This paper describes the application of a modern data mining pipeline, resulting in significant benefits: (1) it applies an exhaustive training process in an iterative manner, exploiting the advantages of significant modern computational services to combine different approaches; in the healthcare field, this strategy results in the utilization of clinical data and development of a trained model acting as the brain of a calculator for the risk of complications in diabetic patients, and (2) it provides a multivariate index of patients' conditions. AI-based strategies were used to input missing data (K-means) and address class unbalance. Models were created considering different prediction approaches and validated through last generation data science principles. Final models demonstrate asymmetry in the predictive performance of each studied complication, suggesting that the variables to be used should be reviewed in detail and differentiated based on each complication to be predicted. A single variable set has limited performance for the prediction of all complications, making it necessary to create pertinent variable groups for each complication.

Also, some limitations need to be recognized. Working with unbalanced classes, which are common in the clinical environment, is a limitation for this type of study because patients presenting a certain condition (incident cases) are in minority. This constitutes a challenge because if a dataset cannot be created with predicting variables based on which ML can differentiate patients, the results obtained could not be used in a clinical environment. Many clinical variables were found to directly correlate with other variables and affect ML performance when included in the model. Variable clearance becomes necessary for avoiding their correlation. Another limitation, and related to retrospective design, is the presence of missing data given that working databases were real-world data collected with other purposes rather than research; although it can be imputed, its clinical feasibility must be demonstrated. Prospective cohorts would be ideal to validate these predictive models.

A key feature is the summarization into variables with repeated measures over time without losing their predictive capacity. Using the CV method, it is possible to synthesize a set of indexed variables to a measurement period preserving their predominance. Before synthesizing repeated measures, data or mistaken clinical measurements need to be cleared and missing values need to be imputed through an adequate segmentation of patients based on variables that have previously been clinically validated as affecting or causing the variable being imputed. Algorithm performance can be assessed with reliable, homogeneously treated, and clinically validated data. The development of predictive models for complications in patients with DM may help assess the correlation between individual factors and a specific complication's onset to consequently stratify the patient for a healthcare center based on that risk and develop tools to support informed clinical decisions regarding treatment.

Future studies should include variables with information on patient lifestyle, such as GPS tracking of the patient's movements, the places visited. Although this may raise controversy in terms of privacy vs. predictive effectiveness, it will enable effective modeling of patient lifestyle and result in highly personalized and effective predictions in addition to clinical data.

Conclusions

ML is a key technology for transforming patient's variables into clinically valuable information through rules developed by medical and engineering experts. This study highlights the ability to predict DM complications, providing valuable support for clinical diagnosis and treatment decisions; ML algorithms can analyze vast amounts of patient data, enabling healthcare professionals to make more informed decisions tailored to individual patients' needs.

The findings of this study emphasize the importance of integrating ML into the field of medicine, as it has the capacity to transform patient data into actionable insights.

By harnessing the power of ML, healthcare professionals can improve patient outcomes, optimize treatment plans, and ultimately enhance the overall quality of care for individuals affected by DM.

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Data Availability Data is available through the corresponding author upon justified request.

Declarations

Competing Interests The authors have no financial or non-financial interests to disclose.

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ORIGINAL ARTICLE

Risk factors associated with severity, prognosis, and evolution of patients with tropical diabetic hand syndrome

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Abstract

Objective Tropical diabetic hand syndrome (TDHS) is rarely described and recognized in the literature as a complication in people with diabetes, and Mexico has high incidence rates of diabetes mellitus II (DMII). The minor or major amputation of the arm represents a physically and economically significant morbidity problem in patients. To optimize the diagnosis and treatment, in this work, we identify prognostic factors and their association with the severity of TDHS and the need for amputation in patients with diabetes mellitus and hand tissue infection.

Methods A total of 55 patients with a confirmed diagnosis of DMII with soft tissue infection in the hand referred to the plastic and reconstructive surgery department were studied for their evaluation and treatment. We analyze sociodemographic and clinical factors and follow-up of remission and recovery in limb functions.

Results In our study, we identified factors associated with amputation such as schooling under 6 years (OR: 21.98, confidence interval (CI): 1.21–3.98, $p=0.003$), body mass index ≥ 20 (OR: 0.07, CI = 0.003–1.41, $p=0.031$), and history of amputation (no upper limb) (OR: 5.9, CI = 1.11–32.1, $p=0.032$). Furthermore, people with TDHS requiring amputation had slightly higher glycated hemoglobin (Hb1Ac) $\geq 10\%$ (OR: 2.36, CI = 0.62–8.98, $p=0.338$), and the risk of death was also increased (OR: 3.4, CI = 0.355–32.6, $p=0.288$), although these outcomes did not reach statistical significance.

Conclusions Risk factors for amputation as a treatment of THDS are directly linked to lower schooling status, poor nutrition/low weight, as well as previous amputation procedures in patients. These data will help to establish a timelier evaluation and management in patients with suspected THDS.

Keywords Tropical hand diabetes syndrome · Diabetes · Hand surgery · Hand infection · Amputation

Introduction

Tropical diabetic hand syndrome (THDS) is a term coined in 1998 by Gill et al. to describe people with diabetes and soft tissue infections affecting the hand and upper limb [1]. Signs ranging from cellulitis and abscesses to gangrene and fulminant sepsis that can end in the death of a patient have been described [2, 3]. People with diabetes have a high risk of peripheral ischemia caused by vascular disease, presenting poor oxygen flow, nutrients, and poor healing in the tissues, which increases the appearance of lesions with frequent infections [1, 4]. Infectious complications due to DM in the hand occur with a ratio of 1:20 compared to diabetic foot [5].

THDS is an important pathological entity in regions such as Africa where 3% of people with diabetes report hand infections [6]. On the other hand, in Western countries, there are no reports of THDS; however, there are hand infections in people with diabetes which are located at 5–7% [7].

Contrary to what its name describes, THDS does not occur exclusively in the tropics, although in those latitudes its prevalence has been extensively reported [8, 9]. Multiple risk factors have been associated with this pathology, low socioeconomic class, type I and II diabetes mellitus, history of trauma or insect bite/sting, peripheral neuropathy, residence in areas near the coast (humid areas), levels of

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glycosylated hemoglobin above 10%, and occupation involving the use of the hand [2, 10–12].

Regarding management, there are no standardized treatment or classification guidelines for THDS, which complicates clinical evaluation. Management algorithms and classifications of lesions have been recently described [5]. The importance of the use of broad-spectrum antibiotics [13, 14], the elevation of the affected limb, and timely debridement of devitalized tissue [2, 11] to control disease progression and avoid complications such as minor or major amputation, which is one of the most recurrent procedures to treat THDS in patients with delayed antibiotic treatment and represents a significant loss of work and economic function for patients [15, 16]. Even some experimental treatments with mesenchymal stem cells to repair skin post-traumatic defects have shown good results [17].

The infections of lesions caused by THDS are usually polymicrobial [13], and the most identified infectious agents are *Staphylococcus aureus* [9, 18], followed by others such as *Streptococcus* spp.[9], *Klebsiella pneumoniae* [19], *Escherichia coli* [11], and *Proteus mirabillis* [18].

Mexico has the second-highest prevalence of obesity and the highest in diabetes mellitus of the member countries of the OECD (Organization for Economic Cooperation and Development), with 15.8% of adults affected, more than double the average of 7% of the other countries [20, 21]. Given the high population risk of developing THDS, the need to optimize the treatments administered is evident to avoid clinical outcomes affecting patients quality of life such as minor or major amputations. To address this issue, in this paper, we focus on evaluating and describing the presentation of THDS in the Mexican population, as well as defining the clinical characteristics to identify the prognostic factors that can help to develop an optimized diagnosis and treatment.

Materials and methods

Study design

This was an observational, prospective, poblational and descriptive study. For this study, all adult patients referred to the Plastic and Reconstructive Surgery Department from 5/1/2021 to 5/1/2023 with a diagnosis of soft tissue infection in the hand and/or forearm and with a diagnosis of Diabetes Mellitus before or during hospitalization were included. Patients who did not have a complete initial assessment on admission and those who could not be located for follow-up, either due to lack of records or information, were excluded from the study. During the study period, 55 patients were recruited. Sociodemographic, paraclinical and clinical data was compilated and follow-up during the consultation to assess remission and recovery of function in the limb were carried out. This study was revised and approved by an institutional ethical committee (Comité de ética e investigación del Hospital Universitario "Dr. José Eleuterio González – Universidad Autónoma de Nuevo León) with the decision reference number CP16-00001.

Evaluation, surgical procedures, and follow-up of patients

The patients were fully evaluated at the time of admission to the hospital for blood pressure, heart rate, respiratory frequency, temperature, weight, and height. The cases were evaluated in conjunction with surgeons specialized in hand surgery to perform a surgical procedure on admissions, such as drainage, debridement, or amputation, and the tissue was sent for culture. In case of chronic wound areas or surgeries, the residents of the Plastic and Reconstructive Surgery service performed the corresponding curation proceedings at intervals and with established healing material depending on the characteristics of the wound.

In addition, during the study period, remission or recurrence of the disease lesions and the evolution of the finger mobility, strength and sensitivity were assessed as soon as the wound showed repair and healing in each patient.

By the time the lesion was completely healed, a 2-point discrimination measurement was performed using the DISCRIMIN-A-GON® (Baseline® Evaluation Instruments, United States of America) following the fabricant instructions, fist strength was measured using a hand dynamometer (B&L Engineering®, United States of America) and the patient sitting in a chair, with armrests, arm at 90°, requesting maximum pressure effort with his hand on 3 consecutive occasions, registering the highest value. Furthermore, clamp strength was assessed using the Jamar® Hydraulic Clamp Force Gauge from Patterson Medical® (United States of America), following the measurement guidelines described by Mathiowetz of adult normative data [22]. Finally, the range of motion of the finger joints was measured using a 6-inch stainless steel Blue Jay™ brand goniometer (United States of America), with the wrist neutral and taking both active and passive measurements, using as normal ranges those described by Mallon in 1991 [23].

Laboratory tests and bacteriological cultures

Laboratory tests and bacteriological cultures were performed using a sterile technique and samples of tissues or secretions from deep compartments were sent.

For the identification of microorganisms, the MALDI-TOF technology was used and for the susceptibility tests, the

isolates were analyzed with the VITEK—2 equipment, using the procedures and parameters validated by the CLSI and the manufacturer. Furthermore, the patients underwent complete biochemical profile studies, as well as the determination of glycosylated hemoglobin (HbA1c).

Statistical analysis

Descriptive data of the study population (age, time since DM diagnosis, infection days, BMI, e,g,) were analyzed using medians and interquartile ranges for quantitative variables and qualitative features such as scholarship, sex, previous amputations, e.g.) were captured as frequency and percentage. Continuous variables were evaluated using the Kolmogorov—Smirnoff normality test to corroborate their distribution. Moreover, risk factors for amputation and risk factors for death in our population with THDS were evaluated using odds ratio tests, using the Fisher´s exact test with 95% confidence intervals and a significance level (α) of 0.05, the data were analyzed using the SPSS version 25.0 software.

Results

Fifty-five patients were included in this study. Descriptive, demographic, and laboratory analysis data appear in Table 1. Briefly, most of our patients were around the fifth or sixth decade of life and presented an average time of diagnosis of DM II of approximately 10 years, in addition, the overall BMI of the population was classified as overweight.

The Glycosylated hemoglobin (HbA1c) median was 10.90 (IQR: 8.4 – 12.28) in the participants treated with debridement and 11.30 (IQR: 10.20 – 13.30) in those treated with amputation. Moreover, our patients treated with debridement reported a median evolution time of the lesions/infection of 12 (IQR 7 – 21) days and 13.5 (IQR 6.25 – 28.5) days for those treated with amputation, leading to patients presenting with injuries and/or severe infections.

Subsequently, we correlate the level of education of the patients with the number of amputations and unfavorable functional results obtained in each group evaluated (Table 2). Our analysis showed that the lower the level of education the patients had, the greater the number of amputations and functional (strength and range of motion) disorders after the surgery recovery were present.

To assess the microbiology of the hand infections of the lesions in our patients, cultures of the lesions were performed (Fig. 1). We were able to analyze cultures from 49 patients, 27 cultures showed single-microorganism isolation, 18 of them (36.73%) showed growth of *Staphylococcus* spp., 13 were classified as *S. aureus,* and 5 as coagulase-negative. In addition, 22 (44.89%) cultures showed polymicrobial growth, of which twelve were able to isolate *Staphylococcus* spp. Were obtained, with a total of 30 patients with this pathogen (59.18%) being the most frequent followed by *Klebsiella* spp. *Streptococcus* spp and *Enterococcus faecalis*.

Regarding the risk factors for amputation, in our group of participants, we were able to find various risk factors associated with limb amputation, such as low schooling (less than high school) (p = 0.003) and presenting a history of previous amputations (p = 0.032). On the other hand, we were also able to find that a body mass index above 20 is associated

Table 2 Level of education and outcome of the lesions in our patients with THDS

Education level		Amputation ($n = 24$)	Abnormal motion AT ($n = 18$)
Illiterate	-	3 (12.5%)	1 (5.55%)
Elementary	Incomplete	8 (33.33%)	6 (33.33%)
	Complete	11 (45.83%)	8 (44.44%)
Junior high school	Incomplete	1 (4.16%)	NA
	Complete	1 (4.16%)	3 (16.66%)
High school	Complete	0	0

AT after treatment, *NA* not assessable due to death before final evaluation

Table 1 Clinical data and laboratory results of studied patients with TDHS

Treatment			
	Debridement ($n = 31$)	Amputation ($n = 24$)	*p*-value
Age, median (IQR)	55 (46–62)	59 (43.5–65.75)	0.9323
Time since DM diagnosis (Months)	96 (6–120)	132 (6–273)	0.1557
Infection evolution prior hospitalization (days)	12 (7–21)	13.5 (6.25–26.5)	0.7075
BMI	27.3 (23.53–29.71)	24.96 (21t.34–29.03)	0.1384
HbA1c (%)	10.90 (8.4–12.28)	11.30 (10.20–13.30)	0.1243
Leucocytes (cel/mm^3)	11.0 (7.95–16.0)	12.35 (10.70–18.18)	0.1082
% Neutrophils	75.20 (64.25–86.0)	79.55 (71.73–87.03)	0.3383
Creatinine (mg/dL)	0.8 (0.6–1.1)	0.95 (0.7–1.57)	0.2230

IQR, interquartile range; *p*-value, Mann–Whitney *U*-test

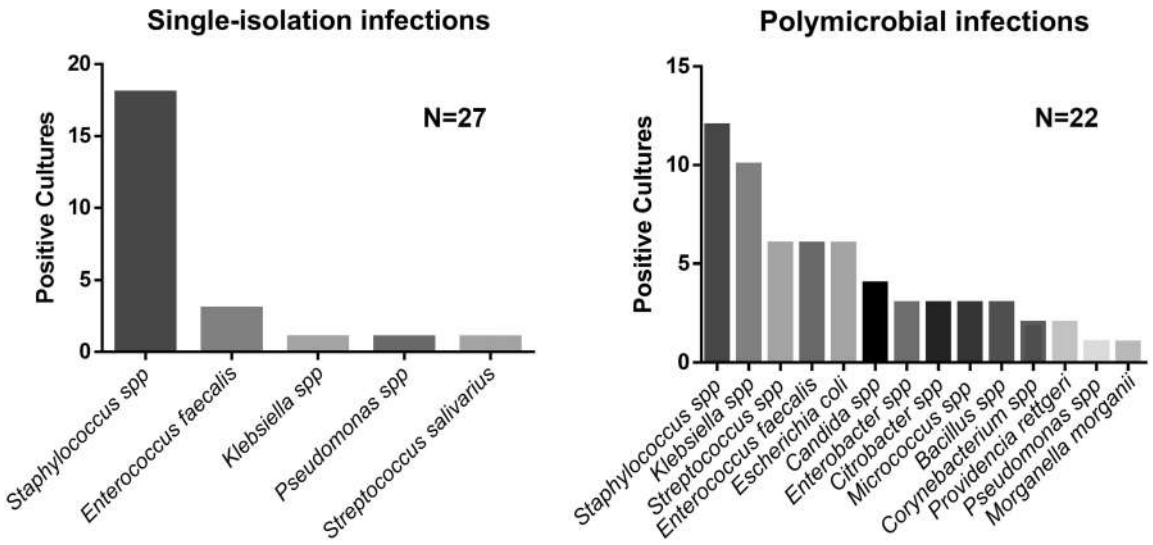

Fig. 1 Identification of the bacteria isolated from the cultures analyzed from the study patients

with a protective effect against amputation (p = 0.031) (Table 3). We did not find any associated risk factor among the variables evaluated for death as an outcome.

In the follow-up evaluations, 19 patients (34.5%) had functional strength alterations, of these, 11 were treated with debridement or abscess drainage, 4 with minor amputation and 4 with major amputation. 20 patients (36.3%) presented alteration in range of motion, 10 of them were treated with debridement or abscess drainage, 6 with minor amputation and 4 with major amputation, no differences between the performed treatment and the type of alterations were found. In addition, eight patients were found to have dysesthesias in the 2-point discrimination assessment. Finally, in our study, 31 (participants were treated by debridement, 24 underwent amputation, of which 13 were minor amputations and 11 major amputations. 5 deaths (9.09%) were recorded, one patient was not cooperative with the clinical assessment, and 5 patients did not attend the final follow-up for assessment of strength and ranges of motion.

Discussion

Tropical Diabetic Hand Syndrome is a poorly defined, complicated, and difficult-to-manage pathological entity, which implies an adequate assessment and timely treatment [11]. There is limited information and updated reports of THDS globally, nevertheless, in our hospital is a frequent pathology, hence, we consider it important to obtain detailed information on this pathology to improve the prognosis and treatment of this disease.

Our population showed that forty-two male patients (76.4%) were attended to and recruited, versus 13 (23.6%) females, which contrasts with reports that showed a greater

Table 3 Risk factors for amputation in the study population of patients with TDHS

	Amputation ($n = 24$)	Debridement ($n = 31$)	OR (CI = 95%)	p-value
Female sex	4 (16.66%)	9 (29.03%)	0.48 (0.13–1.83)	0.349
Handwork	8 (33.33%)	12 (38.70)	0.79 (0.25–2.41)	0.780
BMI ≥ 20	20 (83.33%)	31 (100%)	0.07 (0.003–1.41)	0.031
HbA1c ≥ 10	17 (70.83%)	18 (58.06%)	2.36 (0.62–8.98)	0.338
Scholarship < Junior high	22 (91.66%)	21 (67.74%)	21.98 (1.21–398.9)	0.003
Previous amputations	7 (29.16%)	2 (6.45%)	5.9 (1.11–32.1)	0.032
Neutrophilia	19 (79.16%)	18 (58.06%)	2.74 (0.81–9.26)	0.148
Alcoholism ≥ 30 g/week	8 (33.33%)	7 (22.58%)	1.71 (0.51–5.66)	0.542
Infection ≥ 7 days	7 (29.16%)	6 (19.35%)	1.71 (0.49–6.00)	0.525
Creatinine depuration ≥ 90 mg/dL	12 (50%)	17 (54.83%)	0.82 (0.28–2.39)	0.789

OR odds ratio, *CI* confidence interval, *p*-value, chi-square test

number of patients and increased risk of THDS in females [2, 18, 19]. However, in the countries where these reports were made, a high rate of women workers are employed in manual labor, not so in our population where the role of the manual worker is mostly occupied by men.

In our population, we identify that the level of scholarship of patients is only 6 years or less (elementary education) is a risk factor for amputation. This could be associated with the lack of access to adequate information for the prevention and management of their health conditions, which leads to delays in accessing health services and worse prognoses of the disease [2, 19]. In our patients, the time of evolution of the infection was in a range of 0–90 days, with 11 patients (20%) being those with a month or more of evolution, and 18 patients (32.7%) with less than a week evolution, which increases the severity and depth of the injury, as well as its complexity [11]. In addition, the average BMI of our patients was 27 and only 2 patients had BMI equivalent to malnutrition, this is explained by the high prevalence of obesity in the Mexican population [21] and represents a risk for developing metabolic diseases such as diabetes.

Regarding the risk factors for amputation derived from the hand infection, in our study, we find that a body mass index above 20 is associated with a protective effect against amputation. This correlates with previous reports showing that normal BMI supports limb preservation [2]. However, the higher the BMI, the risk of amputation also increases since it is associated with metabolic alteration. [5]. Likewise, an increased risk of 5.9 times was identified with a history of previous amputation (no upper limb) ($p = 0.032$), limb amputations are associated with people living with diabetes, which may account for the increased risk [2]. Moreover, we identified a risk factor of up to 21.98 times when schooling was less than junior high school ($p = 0.003$). Several studies highlight the need to establish health and nutrition education programs for patients with diabetes to prevent the appearance of THDS, especially in people with poor access to health and education services. [1, 12]. Another important risk factor for developing THDS is glycemic lack of control [11], our patients had HbA1c values of almost 11%, and we observed an increase of up to 3.6 times in the risk of amputation with $HbA1c \geq 10$, however, this data was not statistically significant ($p = 0.338$).

Finally, as in other populations studied, the microbiology of the lesions presented in our patients showed a high prevalence of *Staphylococcus* spp. [1, 24] and multiple polymicrobial infections [13, 18], among which stand out bacterial genera such as *Klebsiella, Streptococcus,* and *Enterococcus*. These data support the theory that these microorganisms are the main ones implicated in this type of infection in patients with THDS.

Limitations of the study

To complement the present study, in the future it is proposed to extend the number of patients studied and carry out a study including control cases that do not present diabetes to more specifically compare the relationship between the aforementioned factors and their association with TDHS. On the other hand, we found an important association between a lower educational level and the development of TDHS; however, this should not be assumed as a causal factor of the pathology and its outcome.

Conclusion

In this study, we showed that factors such as $BMI \geq 20$, previous amputation, and schooling less than junior high school increase the risk of amputation as a treatment in TDHS. Therefore, we suggest that these factors be rigorously taken into account during the approach to patients with THDS for the diagnosis, management, and treatment of hand infections in these patients.

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Data Availability Data collected during this study are available through direct contact with the corresponding author.

Declarations

Ethics approval and consent to participate The authors certify that this work complies with international standards for research practice and reporting. This study protocol was reviewed and approved by the ethics committee of our institution (Comité de ética e investigación del Hospital Universitario "Dr. José Eleuterio González"–Universidad Autónoma de Nuevo León) and the decision reference number is CP16–00001. All informed consent collected during this study was obtained, concisely, legally, and without coercion of any kind.

Conflict of interest The authors declare no competing interests.

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ORIGINAL ARTICLE

Stepping up foot care: assessment over foot care knowledge and behavior among individuals with diabetes of risk levels

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Abstract

Background Diabetic foot is a global threat to public health, as it can lead to infections and amputations and cause significant pain and economic costs for patients. Diabetic foot patients in northern China have more severe local ulcers, worse prognosis, and longer disease duration.

Objective This study assessed the foot risk levels and foot care knowledge and behavior status of people with diabetes with different foot risk levels, and investigated the factors that influence the occurrence of high-risk foot in diabetes.

Methods This cross-sectional survey included 410 hospitalized people with diabetes. Demographic and disease-related data and foot risk stratification status were collected using investigator-designed questionnaires. Foot care knowledge and behavior questionnaires were also used.

Results Among the 410 participants, a total of 367 cases were classified as high-risk feet, among which 135 cases were rated as grade 1, 202 cases grade 2, and 30 cases grade 3. Foot care knowledge surveys revealed low scores in the areas of shoe and sock selection, foot and footwear examination, and management of foot problems. Foot care behavior surveys showed low scores in the areas of foot and footwear examination, management of foot problems, and foot injury risk behavior. One-way ANOVA revealed significant differences in foot care behaviors among patients with different foot risk classifications ($p < 0.05$), while no significant differences were observed in foot care knowledge scores. Multivariate logistic regression analysis showed that age, history of cerebrovascular disease, and foot care behavior scores were factors influencing the occurrence of high-risk foot in people with diabetes.

Conclusion The results of this study showed a high prevalence of high-risk foot in diabetics; The knowledge and behavior of foot care in diabetics with different foot risk levels were both at a moderately low level; There were differences in foot behavior scores among patients with different foot risk classes, but, counter-intuitively, no significant differences in foot care knowledge. The study found that advanced age, history of cerebrovascular disease, and low foot care behavior scores are risk factors for high-risk foot in diabetes. Therefore, it is necessary to screen patients with diabetes for high-risk feet and implement targeted interventions according to the results.

Keywords Diabetic foot · Foot care knowledge and behavior · High risk foot

Introduction

Diabetes is a metabolic disorder characterized by high blood sugar levels and is one of the most common chronic non-communicable diseases worldwide [1]. According to the International Diabetes Federation (IDF) guidelines, there were approximately 537 million people with diabetes worldwide in 2021, and this number is expected to rise to 643 million by 2030 [2]. In China, the prevalence of diabetes in the mainland area is 11.2%, making it the country with the highest number of diabetes patients in the world [3, 4]. Long-term high blood sugar can lead to various diabetes-related complications, particularly in the eyes, kidneys, heart, blood vessels, and nerves, with diabetic foot ulcer (DFU) being the most common and serious [5]. The prevalence of DFU worldwide varies from 1.6% to 8.0% [6], and is estimated to reach 19% by 2045 [7]. DFU is associated with high incidence and mortality rates

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worldwide, with amputation rates as high as 74% for new DFU patients and 5-year mortality rates of 43%~55% [8]. The annual cost of care is approximately 81.7 billion US dollars [9]. The rapid increase in global incidence rates and high treatment costs impose a heavy economic burden on patients, families, and society.

A comprehensive approach to foot care, including prevention, education for patients, multidisciplinary collaboration in managing foot ulcers, and close monitoring, leading to a reduction in amputation rates by 49%~85% [10]. Perrin et al. [11] conducted a cross-sectional survey of 121 patients and divided them into three groups according to their knowledge of DFU development: one group had misconceptions about peripheral neuropathy, another group had a relatively accurate understanding of that, and the third group had no knowledge of foot conditions. The results showed that the group with misconceptions had more potentially destructive foot care behavior than the other groups, indicating that correct knowledge of foot care can guide appropriate foot care behavior and have impacts on foot conditions directly. In addition, physical factors such as wearing inappropriate footwear and socks, improper toenail trimming, and burns account for more than 75% of the factors leading to DFU, and good care can prevent the injuries from occurring [12]. Early identification of high-risk factors for diabetic foot and providing targeted interventions and management is crucial for preventing DFU.

The International Working Group on the Diabetic Foot (IWGDF) 2015 guidelines recommend implementing health education, prevention measures, and follow-up duration according to different foot risk levels [13]. However, previous studies have focused mainly on the overall population of diabetes patients, with little differentiation of DFU risk status among people with diabetes, making it difficult to provide targeted prevention measures based on research findings [14, 15]. Though a recent study failed to find significant difference in foot care knowledge and behavior scores among diabetes patients with different DFU risks [16], the authors suggested further studies be necessary on exploring the foot care knowledge and behavior of people with diabetes with different foot risk levels.

Therefore, this study has three objectives: (1) to assess the foot risk level of people with diabetes; (2) to describe the current status of foot care knowledge and behavior among people with diabetes with different foot risks; (3) to explore the impact of foot knowledge and behavior on high-risk foot occurrence in people with diabetes and other key factors.

Materials and methods

Study design

This is a cross-sectional study using convenience sampling, and including people with diabetes who were hospitalized in the endocrinology department of two tertiary hospitals in northern China between June 2021 and December 2022. All patients who met the inclusion criteria were enrolled in the study.

Inclusion criteria: people with diabetes diagnosed by a regular medical institution according to the 1999 diagnostic criteria of the World Health Organization, aged ≥ 18 years, with normal cognitive function and good communication skills, and willing to participate in the study.

Exclusion criteria: patients who had undergone major amputations (above the ankle), those with severe impairment of heart, liver or kidney function, those with severe diabetic complications, and nondiabetic neuropathy such as central nervous system injury, prolapse of lumbar intervertebral disc, and congenital neuropathy.

Sample size calculation

We used the formula for calculating the sample size of a single rate 95% confidence interval for cross-sectional studies: sample size $N = \left(\frac{Z_{1-\alpha}}{\delta}\right)^2 P(1-P)$.

A previous study [17] indicated that the DFU 60-s screening tool can identify 37% to 48% of diabetic high-risk foot patients. In this study, we selected a p value of 37% and allowed for an error range of ± 5%. The calculated sample size was 359 patients, and a 10% expansion was added, resulting in a final sample size of 395 patients. A total of 410 patients were ultimately enrolled in this study, meeting the sample size requirements.

Data collection tool

The questionnaire used in this study consists of three parts: (1) demographic and disease-related information developed by the investigators. The demographic information includes age, gender, education level, marital status, occupation, smoking, and alcohol intake. The disease-related information includes duration of illness, fasting blood-glucose, other chronic diseases (hypertension, coronary heart disease, COPD, and cerebrovascular disease), history of diabetic foot ulcer and amputation. (2) Foot stratification methods, which were applied according to the IWGDF guidelines and the Guidelines for the Prevention and Treatment of Type [18]. The screening for high-risk diabetic foot includes assessment of peripheral neuropathy, peripheral vascular disease, and foot deformities using various tests such as pressure sensation (10 g monofilament test), vibration perception (128 Hz tuning fork test), ankle reflex, pinprick sensation, temperature sensation, ankle-brachial index (ABI), intermittent claudication, and rest pain. Foot deformities include hallux valgus, toe deformities (such as claw toe, hammer

toe, and mallet toe), metatarsal head protrusion, and post-amputation deformities. Risk stratification is based on the screening results, with Grade 0 indicating low-risk foot and Grades 1–3 indicating high-risk diabetic foot (Table 2). (3) Investigation of knowledge and behavior related to foot care using the knowledge and behavior Foot Care Scale [18], which consists of 17 items related to five aspects of foot care: examination of footwear and socks, foot cleansing and maintenance, selection of shoes and socks, risky behaviors related to foot injuries, and management of foot problems. The total score is converted into a standard score with a range of 0–100, with lower scores indicating poorer knowledge and behavior related to foot care. The reliability of the questionnaire was assessed using Cronbach's α coefficient, which was 0.824 for the knowledge questionnaire and 0.768 for the behavior questionnaire.

Data analysis

The collected data were checked for completeness and coded. Then, the data were entered into EpiData version 3.1 and then exported to SPSS version 24.0 for analysis. Normally distributed continuous variables were presented as mean ± standard deviation, and non-normally distributed continuous variables were presented as median and quartile range. Categorical variables were presented as frequency and percentage. Multiple logistic regression analysis was performed with high-risk foot as the dependent variable and statistically significant variables in the univariate analysis as independent variables. Differences were considered statistically significant if $p < 0.05$.

Ethical consideration

This study has been approved by the hospital's ethics committee, and all participants have provided informed consent and voluntarily participated in the study.

Results

Sociodemographic and disease-related characteristics

Sociodemographic characteristics

The study population was predominantly composed of individuals aged 61 years or older (37.1%), with a roughly equal distribution of men and women (52% and 48%, respectively). Approximately half of the patients had a middle to high school education (48.6%), and most were married (82.2%). The majority of the patients were retired (76.6%) (Table 1).

Disease-related characteristics

The majority of the patients had never smoked (63.4%), and had never alcohol intake (65.6%). The duration of diabetes was mostly greater than 10 years (60.7%), and the fasting blood-glucose was poor control (87.6%). The most common comorbidities were hypertension (55.4%) and coronary heart disease (29.3%) (Table 1).

Diabetic foot risk stratification

Among the 410 patients, a total of 367 (89.5%) were identified as high-risk for diabetic foot, while 43 (10.5%) were low-risk diabetic foot. Specifically, there were 135 (32.9%) patients for grade 1 high risk feet, 202 (49.3%) for grade 2 high risk feet, and 30 (7.3%) for grade 3 high risk feet (Table 2). The results of the three IWGDF screening tests are provided in Table 7 Appendix 1.

Foot care knowledge and behavior status

Foot care knowledge score

The foot care knowledge questionnaire score was 50.65 ± 18.60 (ranging from 5.88 to 94.12). The scores of each dimension in descending order were: foot injury risk behavior, foot cleanliness and maintenance, shoes and socks selection, foot and shoes inspection, and foot problem management (Table 3). The specific scores for each item are shown in Table 8 Appendix 2.

Foot care behavior score

The score of the foot care behavior questionnaire for 410 people with diabetes was 54.46 ± 11.87 (ranging from 19.61 to 86.27). The scores of each dimension, from high to low, were foot cleaning and maintenance, selection of shoes and socks, examination of feet and footwear, management of foot problems, and risky foot behavior (Table 4). The scores for each item in the foot care behavior questionnaire are shown in Table 9 Appendix 2.

Knowledge and behavior status of people with diabetes at different foot risk

Univariate analysis of variance found no statistically significant differences in knowledge scores among people with diabetes at different foot risk levels. However, there was a statistically significant difference in behavior scores ($p < 0.05$) among the different foot risk levels (Table 5).

Table1 Sociodemographic and Disease-Related Characteristics of the study population ($n=410$)

Variables	Categories	Frequency	Percent (%)
Age (years)	≤40	15	3.7
	41 ~	33	8
	51 ~	79	19.3
	61 ~	152	37.1
	71 ~	80	19.5
	> 80	51	12.4
Gender	Men	213	52
	Women	197	48
Education status	Primary school or below	59	14.3
	Junior high school to high school	199	48.6
	University and above	152	37.1
Marital status	No partner	73	17.8
	Have a partner	337	82.2
Occupation	Retired	314	76.6
	On duty	96	23.4
Smoking	Never	260	63.4
	Current	93	22.7
	Former	57	13.9
Alcohol intake	Never	269	65.6
	Current	91	22.2
	Former	50	12.2
Duration of DM	< 5 years	66	16.1
	5 to 10 years	95	23.2
	> 10 years	249	60.7
Fasting blood-glucose	Well controlled	51	12.4
	Poor control	359	87.6
Other chronic diseases			
Hypertension		227	55.4
Coronary disease		120	29.3
COPD		21	5.1
Cerebrovascular disease		52	12.7
History of foot ulcers		30	7.3
History of foot amputation		2	0.5

Table 2 DFU risk stratification ($n=410$)

Grade	Description	Frequency	Percent (%)
0	No neuropathy or vascular disease	43	10.5
1	Only neuropathy	135	32.9
2	Neuropathy combined with vascular disease and/or foot deformity	202	49.3
3	Foot ulcer history or amputation history	30	7.3

*Three patients with vascular disease alone were classified as grade 1

Analysis of risk factors associated with diabetic high-risk foot

Univariate analysis showed that there were statistically significant differences in age, occupation, the history of cerebrovascular disease, foot care knowledge standard score, and foot care behavior standard score between patients with high-risk and low-risk diabetic foot ($p<0.05$), as shown in (Table 6). Using the presence of high-risk diabetic feet as the dependent variable, and the factors that showed statistical significance in the univariate analysis as independent variables, a multiple logistic regression analysis was conducted. Age, the standard scores for foot care knowledge and behavior were used as original values, and the remaining variables were set as dummy variables, with good fasting blood glucose control, retired, and no history of cerebrovascular disease as reference levels. The multiple logistic regression analysis showed that age, the history of cerebrovascular disease, and the foot care behavior score were the influencing factors for people with diabetes to develop high-risk feet (Table 6).

Table 3 Scores of foot care knowledge questionnaire dimensions for patients ($n=410$)

Foot care knowledge dimensions	Standard score ($x \pm s$)	Minimum value	Maximum value	Median
Foot injury risk behavior	71.46 ± 25.39	0	100	75
Foot cleanliness and maintenance	66.04 ± 24.11	0	100	75
Selection of shoes and socks	53.51 ± 20.65	0	100	60
Examination of feet and footwear	50.12 ± 39.79	0	100	50
Management of foot problems	29.88 ± 33.41	0	100	0
Total foot care behavior score	57.50 ± 15.12	11.76	94.12	58.82

The standard score is calculated as (actual score—lowest possible score) / (highest possible score—lowest possible score) × 100

Table 4 Scores of foot care behavior questionnaire dimensions for patients ($n=410$)

Foot care behavior dimension	Standard score ($x \pm s$)	Minimum value	Maximum value	Median
Foot injury risk behavior	13.72 ± 15.33	0	100	8.33
Foot cleanliness and maintenance	58.82 ± 23.74	0	100	58.33
Selection of shoes and socks	48.80 ± 19.84	0	100	53.33
Examination of feet and footwear	35.53 ± 29.88	0	100	33.33
Management of foot problems	15.16 ± 21.04	0	100	0
Total foot care behavior score	54.46 ± 11.87	19.61	86.27	54.90

The standard score is calculated as (actual score—lowest possible score) / (highest possible score—lowest possible score) × 100

Table 5 Knowledge and behavior status of diabetic patients with different foot risk classifications ($n=410$)

Grade	Frequency	Foot Care Knowledge Standard Score	Foot Care Behavior Standard Score
0	43	53.21 ± 17.27	49.70 ± 11.26
1	135	57.95 ± 13.83	54.60 ± 12.08
2	202	58.47 ± 15.43	55.06 ± 11.62
3	30	55.10 ± 14.69	56.60 ± 12.32
F-value		1.733	2.842
p-value		0.16	0.038*

*$p < 0.05$

Discussion

Late complications of diabetes, especially DFU, can lead to amputation, functional decline, increased financial burden for patients, and a sharp decline in their quality of life. Therefore, preventing DFU is necessary. To our knowledge, this is the first such survey conducted in northern China to determine the status of foot care knowledge and behaviors of patients with different DFU risk levels during hospitalization in a tertiary hospital, as well as the related risk factors for high-risk foot development.

In this study, a total of 367 cases of high-risk foot (89.5%) and 43 cases of low-risk foot (10.5%) were screened. Among them, 135 cases (32.9%) were classified as grade 1 high-risk foot, 202 cases (49.3%) were grade 2 high-risk foot, and 30 cases (7.3%) were grade 3 high-risk foot. Compared with previous studies, the overall detection rate of high-risk foot in this study was relatively high [19, 20]. This may be due to the fact that tertiary hospitals in China usually admit difficult and critically ill patients, who are older, have a longer course of disease, and more complications [21]. Screening for high-risk foot as the first step in DFU prevention should be given more attention by healthcare workers. However, in practice, medical staff often pay more attention to patients' blood glucose control and the management of related complications, and insufficient attention is paid to the early screening of high-risk foot. Therefore, in patient education, the importance of high-risk foot screening should be emphasized first. Additionally, it may be related to the increase in screening tools. Previous studies mainly focused on single examinations for high-risk foot screening [22, 23], while the research tool used in this study had more screening items and higher sensitivity, resulting in more cases of neuropathy being detected [18]. Currently, research on high-risk foot screening tools is still in its early stages. Developing a systematic and simple method for high-risk foot screening and making it easy to implement in various settings can better serve people with diabetes for high-risk foot screening.

The results of this study indicate that the knowledge and behavior scores for foot care in people with diabetes were at a moderately low level. In terms of foot care knowledge,

Table 6 Univariate and Multivariable logistic regression analysis for high-risk foot in patients with diabetes ($n=410$)

Variable	Univariate analysis		Multivariate analysis	
	p	OR(95%CI)	*p*	OR(95%CI)
Female	0.716	0.890 (0.475–1.667)		
Age(y)	0.001	1.042(1.018–1.067)	**0.017**	**3.831(1.268–11.578)**
Education status				
Junior high school to high school/Primary school or below	0.160	1.924(0.773–4.792)		
University and above/Primary school or below	0.772	0.880(0.370–2.094)		
Marital status	0.228	0.552 (0.21–1.452)		
Occupation	0.005	0.391(0.204–0.750)	0.236	0.551(0.205–1.476)
Smoking	0.260	1.623(0.699–3.773)		
Alcohol intake	0.769	1.123(0.519–2.431)		
Duration of DM(y)				
5 to 10 / < 5	0.852	1.092(0.432–2.762)		
> 10 / < 5	0.296	1.551(0.618–3.535)		
Hypertension	0.088	1.714(0.923–3.182)		
Coronary disease	0.615	1.195(0.596–2.396)		
COPD	0.354	2.616(0.343–19.966)		
Cerebrovascular disease	0.017	3.831(1.268–11.578)	**0.045**	**8.217(1.047–64.513)**
Fasting blood-glucose	0.096	0.292(0.069–1.244)		
Foot Care Knowledge Standard Score	0.048	1.020(1.000–1.040)	0.474	0.988(0.957–1.020)
Foot Care Behavior Standard Score	0.003	1.040(1.013–1.067)	**0.009**	**1.06(1.015–1.108)**

patients had good knowledge of foot cleaning and maintenance, as well as knowledge of the risk behaviors associated with foot injury. However, their knowledge of shoes and socks selection, examination of feet and footwear, and management of foot problem was insufficient, particularly in terms of knowledge of the need for regular foot checkups at the hospital and applying moisturizing cream after washing their feet. This is similar to the findings of Zheng et al. [24], which showed that patients had limited knowledge of foot care and shoes selection. Due to cultural differences, many Chinese people habitually soak or wash their feet in warm water daily, which may not indicate sufficient knowledge of foot cleaning and maintenance [16]. Therefore, when providing patient education, it is important not only to explain the correct knowledge, but also to inform patients about the harmful effects of incorrect knowledge on the development of DFU, so that patients can consciously accept correct knowledge of DFU and maintain good foot behaviors.

In terms of foot care behavior, patients had good behaviors in foot cleaning and maintenance and shoes and socks selection, but poor behaviors in feet and footwear examination, foot injury behavior, and foot problem management, particularly in terms of patients not being able to visit the hospital for regular foot checkups, not being able to trim their toenails correctly, and wearing slippers in bare feet. This is consistent with the findings of Long et al. [25], which showed that regular foot checkups were the worst behavior of people with diabetes. However, the findings of Maha Obaid Alharbi [26], which indicated that over 50% of patients demonstrated good foot care behaviors, appear to differ from the results of our study. One possible explanation for this discrepancy is the absence of specialized foot clinics in community or general hospitals in China, as well as the lack of regular foot checkups included in diabetes follow-up. As a result, patients mainly rely on their own knowledge and daily habits for foot care, and may not fully appreciate the importance of good foot care behaviors in preventing foot complications. Therefore, it is necessary to provide prevention methods and educational programs for foot ulcers, encourage patients to regularly check their foot condition, and promote the establishment of self-care behaviors.

The results of this study showed no statistically significant difference in foot care knowledge scores among patients with different levels of foot risk, while statistically significant differences were found in foot care behaviors. This may be related to the insufficient emphasis on DFU prevention in various medical institutions in China, and

even if patients develop DFU, medical staff tend to focus more on regulating blood glucose, controlling infection, improving nutrition, and neglecting the impact of preaching foot care knowledge on DFU. In addition, this study found a statistically significant correlation between foot condition and patient age and foot care behavior, indicating that as patients age and their personal knowledge reserves increase, they will pay more attention to blood glucose monitoring and control, and establish good behavioral habits [27]. However, the source of this difference is not that medical staff have health education targeted at patients with different foot risk levels, but rather the natural differences in lifestyle habits that arise as patients' educational levels increase and their disease awareness deepens with age. Therefore, it cannot be assumed that as patients' foot risk levels increase, their foot behavior will improve.

The results of this study showed that age is an important predictive factor for high-risk diabetic foot patients. Other studies have also indicated that people with diabetes over 60 years of age are three times more likely to experience peripheral neuropathy than those under 60 [28, 29]. This may be due to age-related visual impairment, which may limit the ability to conduct normal foot and footwear examinations, as well as the presence of osteoporosis and poor coordination. Therefore, education on foot care should be provided to elderly patients and their families. The results of this study also showed that having cerebrovascular disease is an important risk factor for high-risk feet. This is consistent with the results of a cross-sectional survey that included 62,681 patients [30]. That study showed that cerebrovascular disease, age $\geq$ 45 years, and poor glycemic control were all important risk factors for DFU. This may be due to the fact that people with cerebrovascular disease often have limb sensory impairments, which can lead to delayed diagnosis and treatment. It is recommended that patients with cerebrovascular disease undergo regular foot examinations to assess their risk status and ensure early detection and treatment of foot problems.

In addition, the results of this study show that foot care behaviour scores are also a risk factor for diabetic high risk feet. This finding highlights the importance of patient self-management in preventing complications of DFU. This is consistent with previous research, indicating that foot care practices are crucial for preventing and managing complications of DFU [27]. Relevant studies have shown that the development of foot care education programs can improve foot health outcomes and reduce the incidence of diabetes complications [31]. Therefore, healthcare providers should emphasize the importance of foot care behavior in diabetes management and incorporate this education into their treatment plans to further improve the quality of life of patients .

Limitations

The sample collection for this study was conducted only at two tertiary hospitals in northern China, which may limit the representativeness and generalizability of the findings. In addition, as this study was designed as a cross-sectional study, causal relationships cannot be inferred. Furthermore, due to the short study period, we were unable to diagnose the late outcomes of people with diabetes and observe the progression of their high-risk feet.

Conclusions

The prevalence of high-risk feet in patients with diabetes was found to be high in tertiary hospitals in northern China, with more cases of grade 1 and grade 2 high-risk feet, and poor knowledge of diabetic foot prevention and foot care behavior. We found that age, history of cerebrovascular disease, and foot care behavior score significantly influenced the incidence of high-risk feet in patients. Therefore, it is necessary to strengthen follow-up and education on diabetic foot prevention knowledge for patients who are elderly, suffer from cerebrovascular diseases, and have lower foot care behavior scores. The results of this study can guide the future resource promotion for the most needed groups, thereby helping to reduce the incidence of diabetic feet in adult populations.

Appendix 1

Table 7 Results of the IWGDF Three-Screen Assessment ($n=410$)

Items	Frequency	Percent(%)
Results of Peripheral Neuropathy		
Ankle reflex	117	28.5
Pinprick sensation	127	30.9
Temperature sensation	130	31.6
Vibration perception	108	26.2
Pressure perception	61	14.7
Results of Vascular Lesions		
ABI	75	18.0
Posterior tibial pulse	162	38.8
Dorsalis pedis pulse	35	8.4
Resting pain	35	8.4
Intermittent claudication	61	14.5
Foot Deformities		
Claw toe	17	4.1
Hallux valgus	9	2.2
Prominent metatarsal heads	4	1.0

Appendix 2

Table 8 Scores for each item on the questionnaire assessing knowledge of foot care among patients ($n=410$)

Items	Number of correct responses (n)	Percent (%)
Check feet daily	213	52
Wash feet daily	350	85
Test water temperature before washing feet	298	73
Dry feet thoroughly after washing	332	81
Apply moisturizer after washing feet	177	43
Trim toenails correctly	103	25
Choose shoes in the afternoon or evening	190	46
Wear comfortable shoes	363	89
Check inside of shoes	198	48
Change socks daily	291	71
Choose light-colored socks	158	39
Gradually adapt to new shoes	95	23
Regularly check feet	68	17
Do not walk barefoot	313	76
Do not wear shoes that expose toes	233	57
Do not wear tight socks	346	84
Do not use heating devices	280	68

Abbreviation *DFU*: Diabetic foot ulcer; *IDF*: The International Diabetes Federation; *IWGDF*: The International Working Group on the Diabetic Foot; *ABI*: Ankle-brachial index

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethical approval This study has been approved by the hospital's ethics committee, and all participants have provided informed consent and voluntarily participated in the study.

Conflict of interest The authors declare no conflict of interest.

Table 9 Scores for each item on the questionnaire assessing behavior of foot care among patients ($n=410$)

Items	Scores($x \pm s$)	Never	Occasionally	Often	Always	Better behavior(%)
Check feet daily	2.11 + 1.09	154	127	59	70	31
Wash feet daily	3.29 + 0.90	15	79	90	226	77
Test water temperature before washing feet	2.93 + 1.19	79	68	65	198	64
Dry feet thoroughly after washing	3.05 + 1.18	71	61	55	223	68
Apply moisturizer after washing feet	1.82 + 1.09	228	83	43	56	24
Trim toenails correctly	1.79 + 1.10	240	73	39	58	24
Choose shoes in the afternoon or evening	2.28 + 1.22	157	91	54	108	40
Wear comfortable shoes	3.45 + 0.94	36	23	71	280	86
Check inside of shoes	2.02 + 1.10	183	95	72	60	32
Change socks daily	2.82 + 1.02	48	113	114	135	61
Choose light-colored socks	2.14 + 1.04	136	141	71	62	32
Gradually adapt to new shoes	1.63 + 1.04	279	50	35	46	20
Regularly check feet	1.09 + 0.45	391	10	1	8	2
Do not walk barefoot	3.72 + 0.69	13	16	43	338	93
Do not wear shoes that expose toes	3.32 + 0.91	23	56	99	232	81
Do not wear tight socks	3.58 + 0.87	29	17	50	314	89
Do not use heating devices	3.73 + 0.68	13	15	41	341	93

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ORIGINAL ARTICLE

The effect of prediabetes and diabetes on the incidence of cardiovascular disease in the population of 40 to 70 years in the south of Iran: a population-based cohort study

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Abstract

Objective Diabetes is an important risk factor for cardiovascular disease. The purpose of this study was to explore the role of diabetes and prediabetes in the risk of cardiovascular disease.

Methods This prospective study was performed on three groups of non-diabetic ($n = 7291$), prediabetic ($n = 438$), and diabetic ($n = 1713$) in the age range of 40–70 years in Kharameh (Iran) in 2014–2021. The participants were followed for 4 years. Demographic information, chronic disease history, behavioral habits, and laboratory parameters were examined. Initially, the incidence density was calculated and the difference between the risk of cardiovascular disease in the three groups was examined using the log-rank test. The Cox regression model was performed to investigate the association between prediabetes and diabetes with the risk of cardiovascular disease.

Results The mean age of the participants was 51.47 years. The density incidence in the three groups of non-diabetic, prediabetic, and diabetic individuals was estimated to be 1.5, 1.5, and 3.9 cases per 100,000 person-days, respectively. There was no statistically significant relationship between prediabetes and the incidence of cardiovascular disease. However, the incidence of cardiovascular disease in diabetics was 2.55, 2.16, and 2 times higher than in non-diabetics in the simple, adjusted for age and sex, and in multiple Cox regression, respectively.

Conclusion Due to the independent role of diabetes in the incidence of cardiovascular disease, diabetic individuals should be screened periodically for cardiovascular conditions. Furthermore, it is very important for these individuals to control the important risk factors that contribute to the incidence of cardiovascular disease.

Keywords Incidence · Prediabetes · Diabetes · Cardiovascular diseases · Persian cohort · Iran

Introduction

Diabetes is one of the leading causes of morbidity and mortality worldwide [1]. According to the report by the World Health Organization (WHO), the prevalence of all types of diabetes (type one, type two, and gestational diabetes) has exponentially increased in recent decades. The number of individuals living with diabetes has risen from 108 million in 1980 to 425 million in 2017, and it is predicted that this figure will reach 629 million by 2045 [2]. There are many complications of diabetes. Retinopathy and nephropathy are among the microvascular complications of diabetes,

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and cardiovascular disease (CVD), which is responsible for the morbidity and mortality of many diabetics, is a macrovascular complication of diabetes [3]. In general, CVDs are one of the most serious and important complications in diabetics and prediabetic individuals (a condition in which blood sugar is between normal glycemia and diabetes) [4].

CVDs are disorders of the heart and blood circulation system, of which atherosclerosis (thickening and hardening of the walls of the arteries) is the main cause. These diseases can remain hidden for a long time and appear gradually. The most important causes of atherosclerosis are endothelial dysfunction, inflammatory factors, oxidative, and genetic factors. In general, the interactions of molecular and cellular elements, oxidative stress, and elements of the immune system are known to be effective in the pathophysiology of this disease [5, 6]. CVDs are the leading cause of death worldwide, and many people die from these diseases every year. So that 17.3 million deaths in 2008 were due to CVDs, and it is predicted that this figure will reach 23.6 million by 2030 [7]. In addition, CVDs are one of the leading causes of death in individuals living with diabetes, so the risk of death due to CVDs in diabetics is 3 times higher than in non-diabetics [8], and while diabetics are at high risk of developing these diseases [9].

Due to the clinical burden and complications of CVDs in diabetics and also the role of diabetes in increasing the incidence of CVDs, the focus of health policymakers on the management of diabetic patients has increased. For this reason, developing treatment guidelines is important for the prevention of diabetes and CVDs in diabetic individuals [10]. To be able to make the right decisions in this regard, we need to accurately estimate the incidence of CVDs among patients with diabetes and prediabetes. However, epidemiological studies are limited in this regard and there is no updated information in this field in Iran. Therefore, assessing the current situation regarding diabetes and the risk of developing CVDs will greatly help health policymakers to make more informed decisions to control these diseases. For this reason, this study was performed to investigate the role of diabetes and prediabetes on the risk of CVDs in a population of 40–70 years old in southern Iran.

Materials and methods

Study design

This prospective study was conducted on individuals aged 40–70 years who lived in Kharameh, Fars province (Iran). The Kharameh cohort study is part of a large Persian cohort study in Iran. This study aimed to investigate and identify the risk factors associated with non-communicable diseases in 18 regions of Iran. More details are provided in other articles [11–13].

In the Kharameh cohort study, 10667 individuals aged 40–70 years participated with informed consent (participation rate 97.3%). During the study period, 4 people were lost, and finally, 10,663 people remained in the study. The inclusion criteria included individuals aged 40–70 years who lived in the Kharameh for at least 9 months. This is because during this time they were somewhat adapted to the environmental and cultural conditions that can affect their health. The exclusion criteria for the Kharameh cohort study included individuals with mental disorders, mental retardation, and other untreated diseases and those who were unwilling to participate in the study. The exclusion criteria for this study also included a history of any type of CVDs and a history of heart attack and stroke. Accordingly, 1221 individuals were excluded from the study, and finally, 9442 individuals remained in the study, they were divided into three groups: non-diabetic ($n = 7291$), prediabetic ($n = 438$), and diabetic ($n = 1713$) (Fig. 1).

The baseline data of the Kharameh cohort study were collected from March 2015 to March 2017, and the information about the incidence of chronic diseases in individuals has been collected during four stages of follow-up, in 2018, 2019, 2020, and 2021. Baseline data were collected by trained experts and physicians through face-to-face interviews and using previously validated Persian cohort study questionnaires. The individuals' clinical records according to their self-declaration as well as their medical records were registered. If there was a need to verify the self-declaration of individuals, more diagnostic procedures were performed for them, and they were examined by two physician specialists.

In this study, demographic characteristics including sex, age, occupation, place of residence, marital status, socioeconomic status (SES), and education level were examined. In addition, subjects' behavioral habits including the level of physical activity, alcohol consumption, smoking, and anthropometric characteristics including body mass index (BMI), waist, and hip circumference were evaluated. A history of diabetes, fatty liver disease, and chronic kidney disease (CKD) was also examined. In the present study, fatty liver disease was recorded based on the self-reports of people and the examination of their medical documents (laboratory tests, ultrasound, etc.) by the doctor of the Kharameh cohort team. The laboratory parameters including low-density lipoprotein (LDL), triglyceride (TG), and fasting blood sugar (FBS) were assessed.

Persian cohort questionnaires related to assets were used to assess the SES individuals. The collected data were analyzed using the principal component analysis (PCA) method, and based on the obtained value, the subjects were ranked at four levels: low, moderate, high, and very high. The level of physical activity was also assessed using questionnaires related to daily activities. To determine the level of physical activity of the participants, the collected information

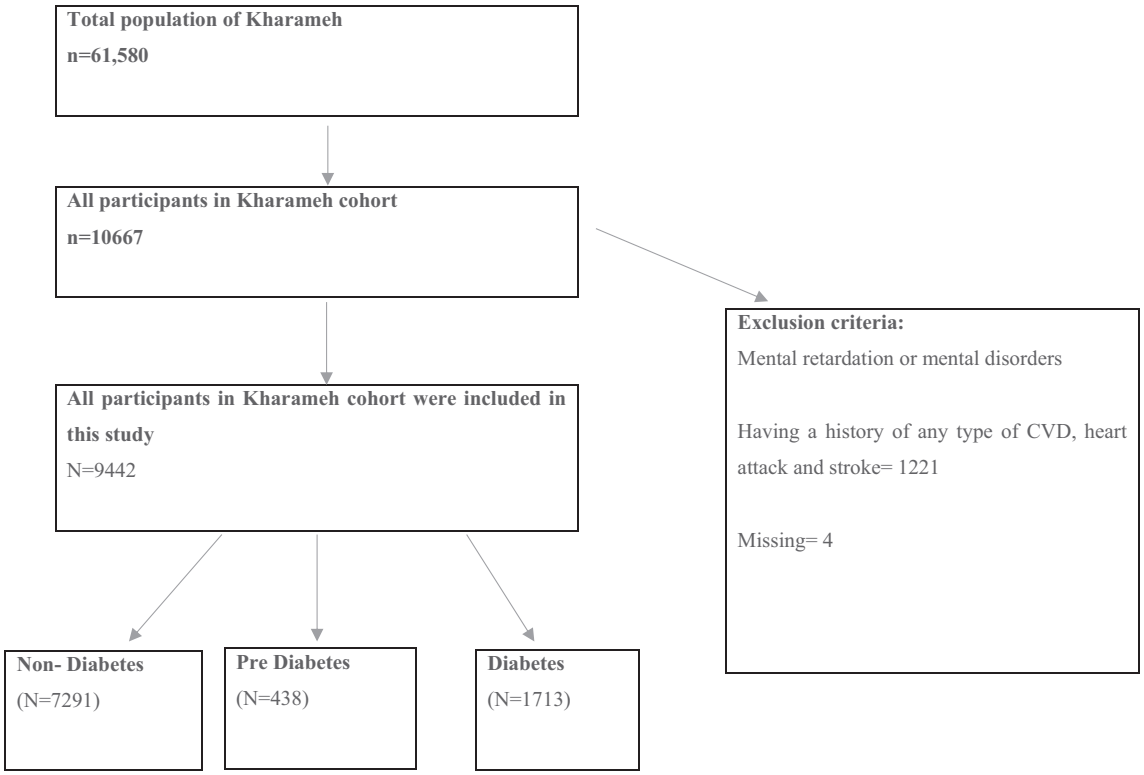

Fig. 1 Flow chart of the study population

was converted into a metabolic equivalent of task (MET) index. Each MET is defined as 1 kcal energy consumed per kilogram (KG) of body weight at rest. Individuals based on the MET index were also divided into four categories: low, moderate level, high level, and severe.

BMI was calculated by dividing weight (KG) by height (m^2), based on which the participants were divided into four categories: (underweight $\leq$ 18.5, normal: 18.5 to 24.9, overweight: 25 to 29.9, and obese $\geq$ 30). The subjects' weight was measured using light clothing and barefoot with a German-made Seca scale, and their height was measured using a standard measuring tape. Blood samples were collected after 12 h without alcohol or cigarette consumption. All samples were measured using the MINDREY branded tool and Pars kit.

Definition of diabetes and prediabetes

Diabetes and prediabetes were defined according to the criteria of the diabetes association in 2020. All individuals with FBS equal to or greater than 6.99 mmol/L (126 mg/dL), and those who had diabetes and were taking medication were considered diabetics in this study. Individuals with FBS between 5.55 and 6.9 mmol/L (110 to 125 mg/dL) were also defined as prediabetic.

In this study, the participants were followed for 4 years, from 2018 to 2021. At each follow-up period, their CVDs status was assessed and their medical records were reviewed by physicians. If physicians confirm the development of CVDs in a person, it is recorded as a new case of CVDs. In this study, CVDs included any type of coronary heart disease, rheumatoid arthritis, cerebrovascular disease, stroke, myocardial infarction, myocardial infarction, and heart valve disease.

Statistical analysis

In the present study, the dependent variable was considered from the time individuals entered the study until the time of the event of CVDs. This interval is calculated based on the number of days. In addition, individuals were considered the right censors if they did not have a CVD event by the end of the study. All demographic variables, behavioral habits, chronic disease history, and laboratory parameters were compared in three non-diabetic, prediabetic, and diabetic groups. Quantitative variables were described by mean and standard deviation, and qualitative variables were described by number and percentage. The normality of quantitative variables was examined by the Kolmogorov-Smirnov test. The density incidence was calculated in three groups. To analyze the survival; Kaplan Meier curve for cardiovascular disease was drawn on three groups of non-diabetic, prediabetic, and diabetic, and the log-rank test was calculated to

compare the survival rate between these three groups. The Cox regression model was used to estimate the effect of the prediabetes and diabetes on the incidence of CVD, in three ways. The first model investigated the effect of prediabetes and diabetes without adjusting for other variables. The second model was adjusted for age and sex variables, and the third model was adjusted for all studied variables with *p*-value less than 0.2 in Cox's simple regression. The power of association was also reported with hazard ratio (HR). All analyses were performed in statistical software for data science(Stata 12) with a significant level of 0.05.

Results

Demographic, clinical, laboratory parameters, and behavioral habits

The present study was performed on 9442 individuals aged 40–70 years. The subjects were divided into three groups: non-diabetic ($n = 7291$), prediabetes ($n = 438$), and diabetic ($n = 1713$). The mean age of the participants was 51.47 ± 8.04 years, which was significantly higher in the diabetic group than in the two groups of prediabetic and non-diabetic (54.5 vs. 51.8 and 50.7 years). Mean TG levels were significantly higher in diabetics than in the other two groups. (150.8 vs. 145.3 and 129.9 mg/dL). The mean waist circumference was significantly higher in individuals with diabetes than in the other two groups. Women made up 65.67% of the diabetics and 57.63% of the prediabetic. In addition, 87.5% of diabetics and 64% of prediabetics were obese and overweight. Almost 30% of diabetics and 21.4 % of prediabetic had low levels of physical activity. Additional descriptive information on demographic characteristics, medical history, behavioral habits, and laboratory parameters is presented in Table 1.

Duration of follow-up and occurrence of cardiovascular disease

In this study, the subjects were followed for 4 years. Non-diabetic individuals were followed for 15,378,504 person-days, prediabetic individuals for 931,980 person-days, and diabetic individuals for 3,434,470 person-days. The density incidence was estimated in non-diabetic individuals with 235 cases of CVD at 1.5 per 100,000 person-days, in the prediabetic group with 14 cases of CVD at 1.5% per thousand person-days, and in the diabetic group with 137 cases at 3.98 per 100,000 person-days (Table 2) displays the incidence curve of CVD in three groups. The log-rank test showed a statistically significant difference in incidence between the three groups (chi2: 84.81 $p < 0.00001$) (Fig. 2).

Association between prediabetes and diabetes with the occurrence of cardiovascular disease

The Cox regression model was performed in three ways to investigate the relationship between prediabetes and diabetes with the incidence of CVDs, in three ways. In all three models, no statistically significant relationship was found between prediabetes and the risk of CVD ($p > 0.05$). However, in the first model, the risk of CVD in diabetics was found to be 2.5 times higher in non-diabetics (HR_{adj}: 2.55 95% CI: 2.06, 3). In the second model, after adjusting for age and sex with a slight reduction, the risk of CVD in diabetics was 2.16 times higher than in non-diabetics (HR_{adj}: 2.16 95% CI: 1.74,2.63); Finally, the third model was adjusted for the variables of age, sex, occupation, marital status, level of physical activity, education, hip circumference, smoking, alcohol consumption, chronic kidney disease, LDL, and TG. The results showed that the risk of CVD among diabetics is 2 times higher than among non-diabetics. (HR_{adj}: 2.03 95% CI: 1.61, 2.55) (Table 3).

Discussion

The present prospective study was performed on 9442 individuals aged 40–70 years in three groups of prediabetic, diabetic, and non-diabetic to evaluate the effect of prediabetes and diabetes on the risk of CVD. After 4 years of follow-up, the density incidence in prediabetic and diabetic individuals was estimated to be 1.5 and 3.9 cases per 100,000 persons-days, respectively. The results of the present study did not show a statistically significant relationship between prediabetes and the risk of CVDs, while diabetes increased the risk of CVDs by 2.5 and 2-fold before and after adjustment of other variables. This indicates the independent role of diabetes in increasing the incidence of CVDs.

Many studies have examined the role of prediabetes in the incidence of CVDs, but their results are inconsistent. In line with the results of our study, a meta-analysis of the cohort studies showed that there was no statistically significant relationship between prediabetes and the risk of CVDs [14]. Prakash et al. also stated that prediabetes was not an independent risk factor for CVDs [15]. Unlike the results of our study, Dorte and colleagues found that the risk of CVDs was twice as high in individuals with prediabetes [16]. Another meta-analysis of 53 cohort studies showed that the risk of developing CVDs in prediabetes was 1.3 times [4]. In addition, another study reported a 1.9-fold higher risk of death due to CVDs in prediabetes [17]. Khosravi and his colleagues believed that the reason for not seeing the relationship between prediabetes and the incidence of CVDs is that prediabetes causes a mild dysfunction of the microvascular and coronary arteries of the heart; therefore, prediabetes cannot cause ischemic heart disease

Table 1 Distribution of baseline characteristics in three groups of individuals with prediabetes, diabetes, and non-diabetes in a population of 40 to 70 years of Kharameh cohort study

Variable	Class	Total ($n = 9442$)	Non-diabetes ($n = 7291$)	Prediabetes ($n = 438$)	Diabetes ($n = 1713$)	p-value
Age		51.47 ± 8.04	50.73 ± 7.87	51.82 ± 8.11	54.51 ± 8.05	0.0001
TG		129.95 ± 31.46	124.15 ± 72.24	145.03 ± 113.36	150.82 ± 98.04	0.0001
LDL		105.32 ± 31.46	105.35 ± 35.86	109.28 ± 28.59	105.84 ± 29.30	0.003
Waist Circumference		95.15 ± 12.03	94.26 ± 12.12	96.45 ± 11.37	98.63 ± 11.1	0.0001
Hip Circumference		100.83 ± 8.43	100.62 ± 8.44	101.25 ± 8.53	101.43 ± 8.33	0.0001
Sex	Male	4192 (44.4)	3418 (48.88)	186 (42.47)	588 (34.33)	0.0001
	female	5250 (55.56)	3873 (53.12)	252 (57.53)	1125 (65.67)	
Job	Unemployed	4400 (46.60)	3145 (43.14)	217 (49.54)	1038 (60.60)	0.0001
	Employed	5042 (53.40)	4146 (56.876)	221 (50.46)	675 (39.40)	
Married status	Single	166 (1.76)	134 (1.84)	13 (2.97)	19 (1.11)	0.0001
	Married	8472 (89.73)	6637 (91.03)	386 (88.13)	1449 (84.59)	
	Divorced	89 (0.94)	76 (1.04)	3 (0.68)	10 (0.58)	
	Widow	715 (7.57)	444 (6.09)	36 (8.22)	235 (13.72)	
Socioeconomic status	Low	2372 (25.12)	1877 (25.74)	99 (22.60)	396 (23.12)	0.291
	Moderate	2634 (27.92)	2077 (27.53)	129 (29.45)	500 (29.19)	
	high	2229 (23.61)	1706 (23.4)	107 (24.43)	416 (24.28)	
	Very high	2205 (23.35)	1701 (23.33)	103 (23.52)	401 (23.41)	
Physical activity	Low	2196 (23.26)	1581 (21.68)	107 (24.43)	508 (29.66)	0.0001
	Moderate	2370 (25.10)	1811 (24.84)	110 (25.11)	449 (26.21)	
	High	2418 (25.61)	1862 (25.54)	109 (24.89)	447 (26.09)	
	saver	2458 (26.3)	2037 (27.94)	112 (25.57)	309 (18.04)	
Education	Illiterate	4793 (50.76)	3547 (48.65)	229 (52.28)	1017 (59.37)	0.0001
	Primary school	2430 (25.74)	1930 (26.47)	119 (27.17)	3881 (22.24)	
	Secondary school	1052 (11.14)	855 (11.73)	34 (7.76)	163 (9.52)	
	High school	735 (7.78)	600 (8.23)	33 (7.53)	102 (5.95)	
	University	432 (4.58)	359 (4.92)	23 (5.25)	50 (2.92)	
Cigarette smoking	No	7083 (75.02)	5349 (73.36)	334 (76.26)	1400 (81.73)	0.00011
	Yes	2359 (24.98)	1942 (26.64)	104 (23.74)	313 (18.27)	
Alcohol consumption	No	8924 (94.51)	6852 (93.98)	420 (95.89)	1652 (96.44)	0.0001
	yes	518 (5.49)	439 (6.02)	18 (4.11)	61 (3.56)	
Location	City	3379 (35.79)	2479 (33.96)	138 (31.51)	765 (44.96)	0.0001
	Village	6063 (64.21)	4815 (66.05)	300 (68.49)	948 (55.4)	
BMI	Underweight	380 (4.02)	342 (4.69)	9 (2.05)	29 (1.69)	0.0001
	Normal	349 (36.99)	2115 (38.61)	149 (34.02)	529 (30.88)	
	Overweight	391 (41.45)	2949 (40.45)	203 (46.35)	762 (44.48)	
	Obese	1165 (17.53)	1185 (72.91)	77 (17.58)	393 (22.94)	
Chronic kidney disease	No	9411 (97.55)	7264 (99.63)	438 (100)	1709 (99.77)	0.426
	yes	31 (0.33)	27 (0.37)	0	4 (0.23)	
Fatty livre	No	8383 (88.78)	6602 (90.55)	384 (87.67)	1397 (81.55)	0.0001
	yes	1059 (11.22)	689 (9.45)	54 (12.33)	316 (18.45)	
Hypertension	No	7634 (80.85)	6188 (84.87)	353 (80.59)	1093 (63.81)	0.0001
	yes	1808 (19.15)	1103 (15.13)	85 (19.41)	620 (36.19)	

[18]. However, some studies have shown that prediabetes may develop into diabetes and this may be a risk factor for CVDs. It is believed that prediabetes can disrupt some of the molecular processes that disrupt the structure of blood vessels, leading to arterial inflammation and vasoconstriction, resulting in the onset of atherosclerosis [18]. It is important to understand that prediabetes is accompanied by microangiopathy and atherosclerotic vascular defect. In addition, prediabetes individuals typically have an older age, obesity, hypertension, and dyslipidemia, which all increase the risk of CVDs [19]. However,

Table 2 Incidence of cardiovascular disease in three groups of individuals with prediabetes, diabetes, and non-diabetes in a population of 40 to 70 years of Kharameh cohort study

	Cases of CVD	Follow-up (person-day)	Incidence (per 100,000 person-day)	Log-rank tests (chi2, *p*-value)
Non-diabetes	**235**	**15,378,504**	**1.5**	84.81 (0.00001)
Prediabetes	**14**	**931,980**	**1.5**	
Diabetes	**137**	**3,434,470**	**3.98**	

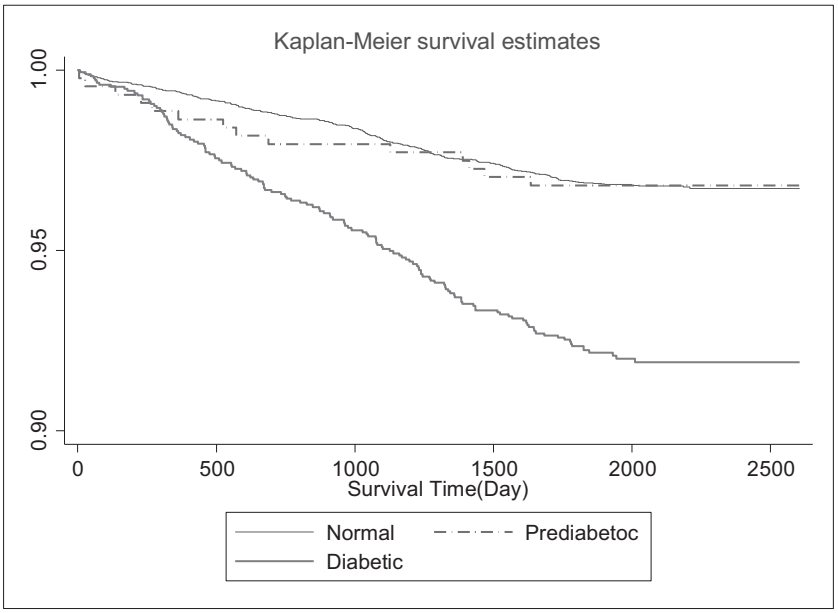

Fig. 2 Kaplan Meier survival curve in three groups of individuals with prediabetes, diabetes, and non-diabetes. Legend: Although the *y*-axis shows the probability of survival between 0 and 1, given that the probability of survival in all three study groups is above 90%, we have only shown the interval 0.9 to 1 for better clarity of the graph

Table 3 The relationship between prediabetes and diabetes with incidence of cardiovascular disease based on the result of Cox regression in a population of 40 to 70 years of Kharameh cohort study

	Model 1		Model 2		Model 3	
	HR_{adj} (95% CI)	*p*-value	HR_{adj} (95% CI)	*p*-value	HR_{adj} (95% CI)	*p*-value
Non-diabetes	1		1		1	
Prediabetes	0.99 (0.57, 1.7)	0.98	0.95 (0.55, 1.64)	0.88	0.95 (0.55, 1.63)	0.853
Diabetic	2.55 (2.06, 3.15)	0.0001	2.16 (1.74, 2.68)	0.0001	2.03 (1.61, 2.55)	0.0001

Model 1: simple Cox regression; Model 2: Cox regression adjusted for age and sex; Model 3: multiple Cox regression adjusted for the variables of age, sex, occupation, marital status, level of physical activity, education, hip circumference, smoking, alcohol consumption, chronic kidney disease, LDL, and TG

these different results can be due to various reasons, including the age of individuals under study, the use of different definitions for prediabetes, and the sample size of different studies. It is also important to keep in mind that in our study, the number of prediabetic individuals was very small, which may be the reason why we do not see the relationship. Therefore, it is necessary to investigate the relationship between prediabetes and CVD incidence more precisely in other studies.

Our study showed a statistically significant relationship between diabetes and the incidence of CVDs, and this has been confirmed by the findings of other studies [20]. Sanne et al. stated that the risk of CVDs in men and women with diabetes was 2.8 and 2.1 times higher than in non-diabetics, respectively [21]. Dorte et al. report that diabetics 54% are more likely to develop CVDs than non-diabetics [16]. Dinesh Shah and colleagues also reported a direct relationship between diabetes and the incidence of CVDs [22]. However, the majority of studies have shown a direct link between diabetes and the risk of CVDs, while CVDs are responsible for half of all cases of death in diabetics [10]. In addition, in the CVD prevention study, it has been shown that the risk of CVDs increases by 9% with each mmol increase in blood sugar [23]. Diabetes contributes to the occurrence of CVDs by causing vascular dysfunction. In general, the mechanism of the effect of diabetes in increasing the incidence of CVDs can be several factors, including endothelial dysfunction, changes in the vessel wall, hyperglycemic toxicity, oxidative stress and inflammation, and

insulin resistance [24]. The pathogenesis mechanisms of CVDs in diabetes are related to genetic, epigenetic, and cell-signaling defects in inflammatory and inter-related metabolic pathways. These metabolic defects (especially in the liver, endothelium, β cells, and skeletal muscle) can be incited by various environmental factors such as smoking, high caloric intake, glucose toxicity, and glycation end-products. Some patients may express mixed or clear phenotypes of hyperglycemia, dyslipidemia, inflammation, hypertension, or thrombosis, which also represent risk factors for CVDs. Diabetes has multiple cell-signaling pathways in survival, cell growth, and proliferation such as AMP-activated protein kinase pathways and pAkt, endothelial nitric oxide synthase pathway, that could potentiate the development of CVDs. In addition to this, oxidized lipids and glucose exert important effects in tissues at the epigenetic level [25].

There are many risk factors for CVDS in diabetics. In fact, these factors are common among diabetes and CVDs. For this reason, we should note that the high prevalence of CVD risk factors (obesity, hypertension, dyslipidemia, etc.) in diabetic people can contribute to the occurrence of CVDs in these people. For example, obesity is known as one of the risk factors for CVDs in diabetic [26]. About 68% of diabetics and 64% of prediabetic in our study were obese and overweight. These factors are one of the most important risk factors for CVDs. In our study, 36.2% of individuals with diabetes and 19.5% of the prediabetics had hypertension. In general, hypertension is a common comorbidity with diabetes that increases the risk of CVDs. Naqipour and her colleagues in their study in the north of Iran stated that control of hypertension in adults reduced the risk of CVDs by 26% [27]. Dyslipidemia disorders are very common in individuals with diabetes and these disorders are an important risk factor for CVDs [26]. The UK prospective diabetes study (UKPDS 23) showed that increased concentrations of low-density lipoprotein cholesterol, decreased concentrations of high-density lipoprotein cholesterol, and systolic blood pressure are the main risk factors for the development of CVDs in diabetic patients [28]. A meta-analysis study showed that treatment with statins to reduce dyslipidemias in 18,000 diabetics resulted in a 13% reduction in the mortality of CVDs [29]. In addition, we must note that the presence of physical and psychological problems can, along with diabetes, worsen the prognosis of cardiovascular events in an individual patient. Ruth and Andrew stated that psychological and social factors in diabetic people potentially affect the risk of CVDs through processes such as reduced physical activity and lifestyle change [30]. Thus, given the presence of many risk factors that lead to CVDs, in individuals with diabetes, it is essential to develop strategies to prevent CVDs in diabetic patients including lifestyle interventions, medication interventions, treatment of hypertension, and anti-diabetic treatment [24]. Lifestyle intervention is also an essential management approach to control these patients so that these interventions can reduce the risk of developing diabetes. Changes in daily activities can also significantly reduce the risk of CVD [4]. In addition, given the importance of this issue, the screening of diabetics for CVD is an important strategy for the reduction of mortality and the incidence of CVDs.

Limitations

This study is a prospective study with a large sample size that was performed under completely standard conditions and examined numerous risk factors. However, the follow-up period of our study was relatively short and the number of individuals with prediabetes was low, which can affect the results of the study. Another one of the limitations of the present study was the lack of access to the status of COVID-19 in the subjects under study. Therefore, we could not investigate the effect of COVID-19 on the development of CVDs in diabetic and prediabetic patients. Also, another limitation of our study was the lack of access to information on the duration of diabetes, which can affect the risk of CVDs.

Conclusion

The results of this study demonstrate that diabetes is an independent risk factor for increasing the risk of CVDs. The high prevalence and rapid growth of diabetes and its complications will lead to an increase in the incidence of CDVs. Therefore, it is necessary to carry out effective interventions for the timely identification of people with diabetes and also to control diabetes in them. In addition, due to the high prevalence of CVD risk factors in diabetics, lifestyle change education to reduce modifiable risk factors in them can help reduce the incidence of CVDs.

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Author contribution R.A was responsible for the fieldwork including data collection and management. M.L did the analysis and wrote the method and parts of the manuscript. H.SV collected data. S.M checked all analyses, graphs, and tables and managed how to analyze them. Gh.M and H.SV also wrote the part of the manuscript.

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Data availability Not applicable.

Declarations

Ethics approval This research is extracted from a Ph.D. dissertation under the supervision of Dr. Abbas Rezaianzadeh. It has also been approved by the ethics committee of Shiraz University of Medical Sciences. (IR.SUMS.SCHEANUT.REC.1400.046)

Consent to participate Not applicable.

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Competing interests The authors declare no competing interests.

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ORIGINAL ARTICLE

Prevalence of thyroid nodule and its association with β-cell autoantibodies in adult patients with type 1 diabetes mellitus without thyroid dysfunction

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Abstract

Objective Although many studies have shown the relationship between type 1 diabetes mellitus (T1DM) and autoimmune thyroid diseases, few studies have conducted a morphological evaluation of the thyroid gland in T1DM without thyroid disease. This study aimed to compare thyroid ultrasonography findings of the healthy control group with the T1DM group without thyroid disease and examine the relationship between β-cell autoantibodies and the presence of thyroid nodules.

Methods This cross-sectional study included 119 patients with T1DM and 105 healthy controls. Thyroid function tests, thyroid volume, and presence of thyroid nodules were compared between the two groups. Patients with T1DM were divided into two groups according to the presence of thyroid nodules, and risk factors that may affect the development of thyroid nodules were tried to be determined.

Results No significant difference was found between the control group and the T1DM group in terms of thyroid function tests, thyroid volume, and presence of thyroid nodules. In the T1DM group, the number of female patients and the islet cell antibody (ICA) positivity rate were higher in the presence of thyroid nodules. As a result of regression analysis, ICA positivity in the T1DM group increased threefold the risk of having thyroid nodules.

Conclusion A relationship was observed between ICA positivity and thyroid nodules in T1DM. Thus, cases with ICA positivity may have a higher probability of nodules in the thyroid gland, and neck examinations should be performed more frequently.

Keywords Auto immune thyroid disease · Islet cell antibody · Type 1 diabetes mellitus · Thyroid nodule

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Introduction

Type 1 diabetes mellitus (T1DM) is a chronic disease with absolute insulin deficiency caused by the destruction of beta cells in the pancreas [1]. According to the International Diabetes Federation (IDF), 10.5% of the adult population worldwide has DM, and approximately 10% of this is T1DM [2]. According to the IDF data, the T1DM prevalence in Turkey's 0–14 age group has increased approximately 2.48-fold in the last 20 years [2].

Autoimmune thyroid disease (AITD) and T1DM are common autoimmune disorders worldwide. The relationship between T1DM and AITDs has been reported in many studies. While the incidence of AITD ranged from 7 to 50% in different studies of patients with T1DM, the incidence of AITD was 10% in non-diabetic individuals [3–5]. Both diseases are T-cell-mediated chronic disorders and have a similar pathogenesis, comprising T-cell infiltration resulting in the dysfunction of the pancreas or thyroid gland. Thyroid peroxidase autoantibodies (TPO-Ab) are present in 7–36% of adults with T1DM, and long-term follow-up suggests that 30% of the patients with T1DM will develop AITD [5]. The relationship between thyroid volume and nodule prevalence in T1D patients with AITD is complex. Some studies have suggested that individuals with T1D and AITD may have an increased risk of thyroid enlargement and thyroid nodules compared to those with AITD alone [6–8]. Various factors may influence these findings, including the specific type and severity of AITD, thyroid functions, genetics, and environmental factors.

A few population studies have focused on thyroid nodularity in patients with T1DM without AITD. Etiological factors such as female sex, iodine deficiency, smoking, genetic factors, and thyroid volume are the main causes of thyroid nodule formation in the thyroid gland [9]. Moreover, knowledge on T1DM and thyroid nodularity in adults is limited, as most studies included children and adolescents. To date, available data demonstrated inconsistent results about thyroid morphology in patients with T1DM [7, 8, 10–12].

Thus, this study aimed to evaluate thyroid morphology through ultrasonography (USG) in patients with T1DM without thyroid dysfunction in comparison with those of age and sex-matched healthy controls and investigate the relationship between pancreatic autoantibodies and thyroid nodularity in patients with T1DM.

Material and methods

Study design

The study included 119 patients who were diagnosed with T1DM at the University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital, Department of Endocrinology and Metabolism between January 2015 and April 2019 and 105 healthy controls. The study was conducted as a cross-sectional study among healthy controls and patients with T1DM. The study protocol was approved by the ethics committee of our center. The study was conducted in accordance with the Declaration of Helsinki.

Participant files were scanned for age, sex, body mass index (BMI), and DM duration. The hemoglobin A1C (HbA1c), fasting plasma glucose (FPG), thyroid-stimulating hormone (TSH), free thyroxine (fT4), and free triiodothyronine (fT3) levels recorded in the last clinic visit were obtained from the medical records. In the T1DM group, three β-cell autoantibodies including glutamic acid decarboxylase antibody (GADA), islet cell antibody (ICA), and insulin autoantibody (IAA) were tested in our center. The levels of β-cell autoantibodies performed during the T1DM diagnosis were used in the analyses. Adult patients aged 18–50 years with a diagnosis of T1DM for at least 1 year, negative thyroid autoantibodies, normal thyroid functions, and no known thyroid disease were included in the study. Patients with other types of DM, patients with positive thyroid autoantibody or abnormal thyroid function tests (overt/subclinical hypo-hyperthyroidism), pregnant or breastfeeding, patients with unavailable biochemical parameters or ultrasonographic findings, and patients using drugs that disrupt thyroid function tests, were excluded from the study. The control group was established by selecting patients who were compatible with the T1DM group in terms of age-sex among healthy individuals who had a T1DM in their relatives, who applied to our hospital for control, and whose examinations did not detect any disease. Thyroid autoantibodies of the control group were negative. In addition, β-cell autoantibodies of individuals in the control group with T1DM in first-degree relatives were evaluated, and patients with negative autoantibodies were included in the study. None of the controls had thyroid diseases or acute illnesses, and none of them were using any medication that affected their thyroid functions. All participants were consuming iodized salt. The flow chart of the study population is shown in Fig. 1.

Clinical and biochemical measurements

BMI was calculated as the weight in kilograms divided by the height in meters squared. The assays were performed in the laboratory of our center. Evaluations were conducted for HbA1c, FPG, thyroid function, anti-thyroid peroxidase antibody (anti-TPO), anti-thyroglobulin antibody (anti-Tg), and β-cell autoantibodies. HbA1c was measured using the high-performance liquid chromatography method (Bio-Rad

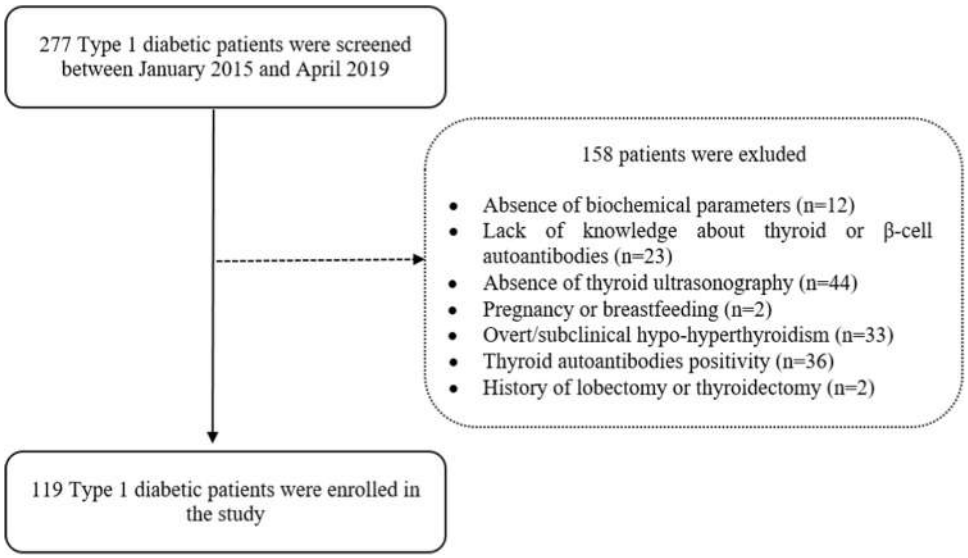

Fig. 1 Flow chart of the study population

Variant-2, Tokyo, Japan). Tests for thyroid function and thyroid antibodies were performed with the chemiluminescent immunoassay (Beckman Coulter, CA, USA). Radioimmunoassay was used to measure β-cell autoantibody levels as GADA, ICA, and IAA (Stratec-Gama Reader RIA Mass, Birkenfeld, Germany). Reference ranges were defined as follows: TSH, 0.38–5.33 uIU/mL; fT3, 2.28–4 pg/mL; and fT4, 0.60–1.25 ng/dL. The reference range for anti-TPO and anti-Tg were 0–1.5 IU/L, 0–35 IU/mL, and 0–40 IU/mL, respectively. Normal ranges of islet cell autoantibodies were as follows: <1 U/mL, negative; 1–2 U/mL, borderline; >2 U/mL, positive; for ICA, <1 U/mL, negative; 1–2 U/mL, borderline; >2 U/mL, positive; for GADA, $<8.2\%$, negative; and $>8.2\%$, positive for anti-IAA. Thyroid and islet cell autoantibodies were considered positive if they were above the reference range. Sonographic thyroid measurements were performed by an experienced endocrinologist in the supine position with the hyperextended neck. Thyroid USG was performed using high-resolution B-mode ultrasound (EUB 7000 Hitachi® HI VISION, Tokyo, Japan) with a 13-MHz linear array transducer. Transverse and longitudinal scans were performed by USG to measure the depth, width, and length of each lobe. The volume of the thyroid gland was calculated using the ellipsoid formula (mL) (length (cm) × width (cm) × thickness (cm) × π/6). The total thyroid volume was the sum of the volumes of both thyroid lobes, excluding the volume of the isthmus.

Thyroid nodules were grouped according to the European Thyroid Imaging and Reporting Data System (EU-TIRADS) classification based on their ultrasonographic features [13]. The EU-TIRADS scores are as follows: EU-TIRADS 1, no nodule; EU-TIRADS 2, pure cystic or spongiform nodules; EU-TIRADS 3, ovoid, smooth, isoechoic, or hyperechoic nodules; EU-TIRADS 4, ovoid, smooth, mildly hypoechoic nodules without high-risk suspicious features; and EU-TIRADS 5, nodules that have any of the suspicious high-risk features (irregular margin, taller than wide, microcalcification, and markedly hypoechoic). All fine-needle aspirations (FNAs) were performed in our clinic, and the FNA decision was based on EU-TIRADS risk stratification. FNA was performed for nodules of >20 mm without high-risk suspicious features in EU-TIRADS 3. FNA was performed for nodules >15 mm in EU-TIRADS 4. FNA was performed if the nodule size was >10 cm in EU-TIRADS 5. If the nodule size is <10 cm, active surveillance or FNA was performed according to the patient's decision. FNA cytology was reported in accordance with the Bethesda classification [14]. The Bethesda system is divided into six categories as follows: I, nondiagnostic; II, benign; III, atypia of undetermined significance/follicular lesion of undetermined significance; IV, follicular neoplasm/suspicious for follicular neoplasm; V, suspicious for malignancy; and VI, malignant.

Statistical analysis

Collected data were analyzed statistically using IBM SPSS Statistics software version 23.0 (IBM Corp., NY, USA). Categorical data, such as sex, presence of thyroid nodules, and autoantibody positivity, were expressed with frequencies and percentages. Data were preliminarily analyzed with the Kolmogorov–Smirnov test for compliance with the normal distribution. Descriptive statistics are presented as mean ± standard deviation for continuous data with normal distribution. Continuous variables with non-normal distribution were presented as median (range) values. Initially, the participants were divided into two groups: the T1DM group and the control group. Demographic data, thyroid function tests, thyroid volume, and presence of thyroid nodules were compared between the two groups. Then, patients with T1DM were divided into two groups according to the presence of thyroid nodules in the thyroid gland, and

the relationship between the presence of nodules and islet cell autoantibodies was analyzed. The independent two-sample *t*-test was used to analyze continuous data with normal distributions. The Mann–Whitney *U* test was used to analyze non-normally distributed data. The differences between categorical variables were analyzed by Chi-square analysis. Univariate and multivariate regression analyses were performed to evaluate the relationships between the presence of thyroid nodules and islet cell autoantibodies in the T1DM group. First, univariate logistic regression analysis was used to determine the variables affecting the presence of thyroid nodules in the T1DM group. Then, multivariate logistic regression analysis was performed using variables found to increase the risk of thyroid nodule development in the univariate logistic regression analysis. A p value of <0.05 was considered statistically significant.

Results

A total of 119 patients diagnosed with T1DM and 105 healthy adults were enrolled in the study. The T1DM comprised 65 (54.6%) women and 54 (45.4%) men with a mean age of 30.7 ± 8.7 years. The control group comprised 70 (66.7%) women and 35 (33.3%) men with a mean age of 32.4 ± 9 years. The median DM duration was 8 (1–27) years. GADA, ICA, and IAA positivity in T1DM patients were 36.97% ($n=44$), 44.5% ($n=53$), and 8.4% ($n=10$), respectively. The mean BMI was 23.1 ± 3.6 kg/m^2 in the T1DM group and 24.3 ± 2.8 kg/m^2 in the control group. No statistically significant difference was found between the groups in terms of age, BMI, and sex. The full demographic and clinical data of the T1DM group and the control group are presented in Table 1.

In the T1DM group, TSH, fT4, and fT3 levels were 1.8 ± 0.8 mIU/L, 1 ± 0.2 ng/dL, and 3.2 ± 0.4 ng/dL, respectively. In the control group, the TSH, fT4, and fT3 levels were 2 ± 0.9 mIU/L, 1 ± 0.2 ng/dL, and 3.3 ± 0.4 ng/dL, respectively. The thyroid volume was 13.5 ± 6.2 cm^3 in the T1DM group and 14.4 ± 10.7 cm^3 in the control group. Thyroid nodules were observed in the thyroid gland in 30.2% ($n=36$) of patients in the T1DM group and 38% ($n=40$) of the participants in the control group. No significant difference was found between the two groups regarding thyroid volume, thyroid function tests, and presence of thyroid nodules ($p>0.05$).

The EU-TIRADS scores of 36 thyroid nodules are demonstrated in Fig. 2. FNA was performed in 8 (22.2%) of 36 thyroid nodules detected in the USG according to ultrasonographic

Table 1 Full demographic and clinical data of patients with T1DM and controls

	T1DM ($n=119$)	Control ($n=105$)	p
Age (year)	30.7 ± 8.7	32.4 ± 9	0.152
Sex (F/M)	65/54	70/35	0.066
BMI (kg/m^2)	23.1 ± 3.6	24.3 ± 2.8	0.218
FPG (mg/dL)	256.9 ± 123.5	88.2 ± 8.7	<0.001
HbA1c (%)	10.8 ± 3	5.5 ± 0.3	<0.001
TSH (mIU/L)	1.8 ± 0.8	2 ± 0.9	0.057
fT4 (ng/dL)	1 ± 0.2	1 ± 0.2	0.655
fT3 (ng/L)	3.2 ± 0.4	3.3 ± 0.4	0.510
Thyroid volume (cm^3)	13.5 ± 6.2	14.4 ± 10.7	0.438
Presence of nodule (%)	30.2	38	0.245
Size of thyroid nodule (mm)	8 (3–38)	6 (2–44)	0.205
EU-TIRADS			
EU-TIRADS 1	83	65	
EU-TIRADS 2	23	26	
EU-TIRADS 3	9	6	0.31
EU-TIRADS 4	1	5	
EU-TIRADS 5	3	3	
Bethesda classification			
Bethesda 1	2	2	
Bethesda 2	3	8	0.6
Bethesda 3	1	1	
Bethesda 5	2	1	

BMI body mass index, *F* female, *FPG* fasting plasma glucose, *fT3* free triiodothyronine, *fT4* free thyroxine, *M* male, *T1DM* type 1 diabetes mellitus, *TSH* thyroid-stimulating hormone, *EU-TIRADS* European Thyroid Imaging and Reporting Data System

features. The FNA results were Bethesda I, II, III, and V in 2, 3, 1, and 2 patients, respectively (Fig. 3). FNA was repeated for three patients with Bethesda 1 and 3 and reported as benign cytology. Two patients whose FNA reported as Bethesda 5 underwent total thyroidectomy. The pathology result of both patients was papillary thyroid carcinoma. The rate of papillary thyroid carcinoma was 1.7% of the thyroid nodules observed in patients with T1DM without thyroid disease.

Patients with T1DM were divided into two groups according to thyroid nodularity (Table 2). No significant difference was found between the two groups in terms of age, DM duration, BMI, thyroid function tests, HbA1c, FPG, and thyroid volume. In the group with thyroid nodules, the proportion of female participants was statistically significantly higher (72.2% vs. 47%, $p=0.011$). ICA positivity was higher in the group with thyroid nodules (63.9% vs. 36.1%, $p=0.005$). Anti-GAD and anti-insulin autoantibody positivity rates were statistically similar between the two groups. As a result of regression analysis, the presence of thyroid nodules was threefold higher in patients with T1DM who were positive for islet cell autoantibodies (Table 3).

Discussion

This cross-sectional study did not find a difference in thyroid function tests, thyroid volume, and presence of thyroid nodules between T1DM patients without AITD and age- and sex-matched controls. When patients with T1DM were divided into two groups according to the presence of thyroid nodules, the number of female participants and the ICA positivity rate were higher in the group with thyroid nodules. As a result of the regression analysis, only ICA was associated with the presence of thyroid nodules.

Gomez et al. reported that basal TSH levels of patients with T1DM without AITD were generally similar to the healthy population [15]. A few studies involving patients with AITD reported that patients with DM had lower serum FT3 levels than those without DM [7, 10]. In a study conducted in Italy, including patients without overt thyroid disease but positive for thyroid autoantibodies, fT4 levels were higher in the T1DM group than in the control group [8]. Compared with other studies, the present study excluded patients with overt thyroid disease and/or high thyroid

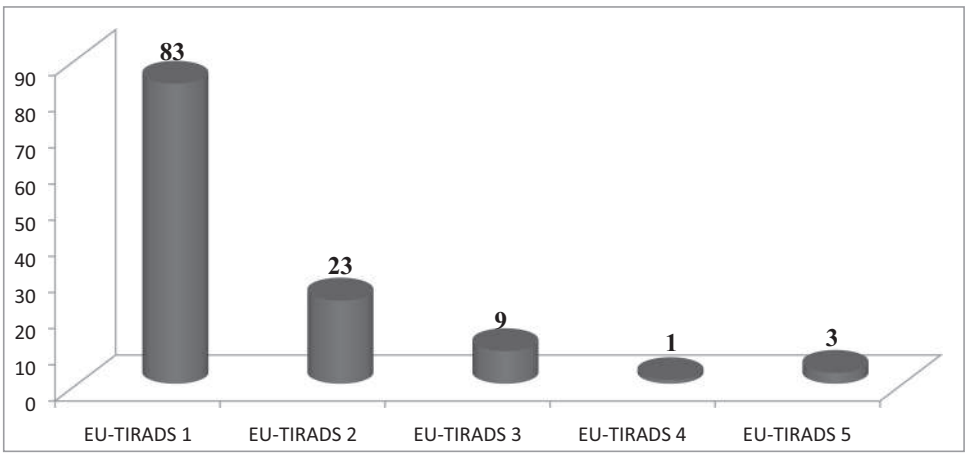

Fig. 2 European Thyroid Imaging and Reporting Data System (EU-TIRADS) scores of the thyroid nodules

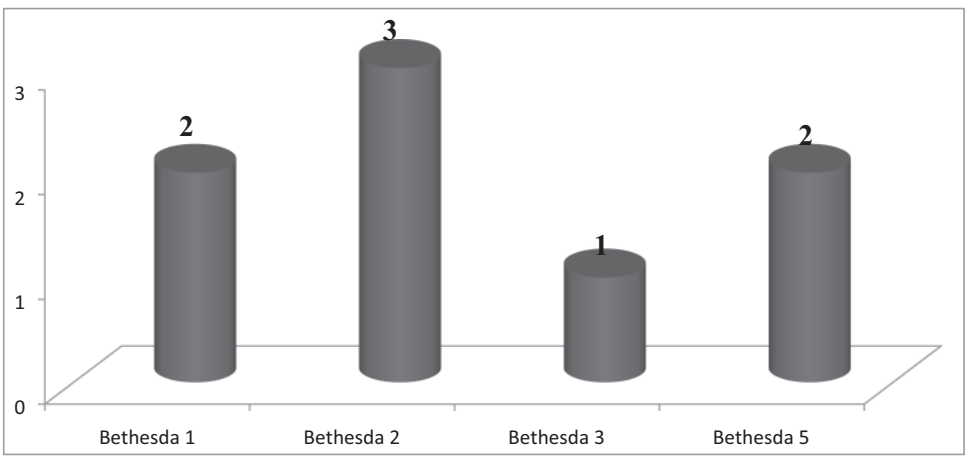

Fig. 3 Bethesda classification of thyroid nodules undergoing fine-needle aspiration

Table 2 Comparison of T1DM patients with and without thyroid nodules

	Presence of nodule ($n=36$)	Without nodule ($n=83$)	p
Age (year)	31.9 ± 11	28.9 ± 7.3	0.105
Sex (F/M)	26/10	39/44	0.011
BMI (kg/m^2)	23.7 ± 3.1	21.9 ± 3	0.151
Diabetes duration (year)	13 (1–27)	7.5 (1–27)	0.142
FPG (mg/dL)	281.9 ± 134.1	244.4 ± 112.6	0.142
HbA1c (%)	10.8 ± 2.7	10.8 ± 3	0.909
TSH (mIU/L)	1.6 ± 0.7	1.8 ± 0.9	0.283
fT4 (ng/dL)	0.98 ± 0.16	1 ± 0.2	0.403
fT3 (ng/L)	3.1 ± 0.5	3.3 ± 0.4	0.301
Thyroid volume (cm^3)	14.3 ± 5.4	13.1 ± 6.5	0.371
GADA positivity (%)	33.3	38.6	0.59
IAA positivity (%)	8.3	8.4	0.99
ICA positivity (%)	63.9	36.1	0.005

BMI body mass index, *F* female, *FPG* fasting plasma glucose, *fT3* free triiodothyronine, *fT4* free thyroxine, *GADA* glutamic acid decarboxylase antibody, *IAA* insulin autoantibody, *ICA* islet cell antibody, *M* male, *TSH* thyroid-stimulant hormone

Table 3 Results of the logistic regression analysis performed on patients with type 1 diabetes mellitus for the presence of thyroid nodule

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
ICA positivity	3.1 (1.1–8.5)	0.024	3 (1.08–8.3)	0.03
Sex	3 (1.2–7.6)	0.014	2.64 (0.91–7.65)	0.075
Diabetes duration	1.050 (0.991–1.11)	0.098		

ICA islet cell antibody, *OR* odds ratio

autoantibody levels, and the effect of T1DM on thyroid function tests was evaluated independently of autoimmunity. Thyroid function tests of patients with T1DM were found to be similar to the control group.

The results of studies evaluating thyroid volume in patients with T1DM are controversial [7, 8, 10–12, 15–17]. In most of the previous studies, the total thyroid volume was higher in the T1DM group than in the control group [7, 8, 15]. The possible explanation for these findings is the higher prevalence of AITD and hyperinsulinism in their studies and the proliferative effect of these on the thyroid gland. On the contrary, Darendeliler et al. and Hansen et al. did not observe any statistically significant difference in the thyroid volume between the T1DM group and the control group [11, 12]. This is probably due to the fewer incidences of AITD among the studied patients with T1DM. Gomez et al. found that fat-free mass is different between the T1DM group and the control group, and they proposed that the body surface area and fat-free mass are the main determinants of thyroid volume [15]. Okten et al. reported that the thyroid volume in patients with DM was related to BMI and age without any relation to urinary iodine excretion and thyroid hormones [7]. Comparing the volume findings in the present study with those in previous studies is difficult because of the differences in anthropometric measurements, age distribution, iodine status, and thyroid autoimmunity. In the present study, the thyroid volume of patients with T1DM was similar to age- and sex-matched healthy controls. This result can be attributed to the exclusion of patients with autoimmune/non-autoimmune thyroid disease in the DM group, the older age of the patients with DM, adequate iodine status, and shorter median DM duration.

Nodule formation in the thyroid gland is a common entity and is detected in approximately 2–6% of the adult population by physical examination alone [18]. In surveys using USG, 19–76% of women had at least one thyroid nodule [18–21]. In a study conducted in Germany, thyroid nodules or goiter were found in 32% of women and 33% of men with 96,278 scanning ultrasound images [22]. Most studies have reported a significant relationship between large thyroid volume and the presence of nodules [9, 23]. Dauksiene et al. found that female gender, higher TSH levels, and thyroid volume were independent risk factors for the presence of thyroid nodules [9]. Larger thyroid volume may be a risk factor for thyroid nodules due to increased cell proliferation [24, 25]. A larger thyroid gland may have a higher number of thyroid follicular cells. These cells can undergo abnormal proliferation, increasing the chances of one or more cells developing into nodules. In addition, some individuals may have a genetic predisposition to develop thyroid nodules [26]. A larger thyroid gland may provide more tissue for these nodules to form in such cases. In the present study, thyroid nodules were detected in the thyroid gland by USG in 38% of the patients in the control group, similar to the literature. Few studies are reporting the prevalence of thyroid nodules in patients with T1DM. The incidence of thyroid nodules in patients with T1DM ranges from 10 to 19% [10, 27]. The higher rate of nodular goiter in the present study could be due to the higher performance, in terms of the quality of the image, of the USG instruments. Völzke et al. found that patients with T1DM had a higher risk of known thyroid disease and a lower risk of goiter and thyroid nodules than the reference population [10]. The inclusion of patients with known thyroid disease in the study and the median DM duration of 14 years may have resulted in different results from our findings. The results of the present study show that the prevalence of thyroid nodules is not increased in patients with T1DM

without thyroid disease (autoimmune or non-autoimmune) compared with control participants.

ICA is usually present in the diagnosis of T1DM and is expected to decrease in level and frequency in the later years of the disease [28, 29]. Previous studies have reported an increased prevalence of GADA, IA-2A, and ZnT8 autoantibodies in patients with T1DM and AITD, indicating a potential association between thyroid autoimmunity and β-cell autoantibodies [30, 31]. Moreover, a novel finding was that the rate of ICA positivity in patients with T1DM without thyroid disease was much higher in patients with thyroid nodules. In the current study, when regression analysis, including the duration of diabetes, was performed, it was found that nodules were more common in patients with T1DM who were positive for ICA, independent of the duration of diabetes. This result indicates that the ongoing autoimmune process in T1DM may cause morphological changes in the thyroid gland without any AITD signs. A possible reason for this is that GADA, IA-2A, and ZnT8 autoantibodies are mostly specific to pancreatic β-cells, but ICA is expressed in neuroendocrine organs in addition to pancreatic islet cells.

Although patients with T1DM have increased risks of stomach, liver, pancreas, and endometrial cancer, little is known about the risk of papillary thyroid carcinoma [32–34]. A few studies have investigated the relationship between T1DM and thyroid cancer, and their results are controversial [33–35]. A study conducted in Sweden reported that 1.2% of patients with T1DM were diagnosed with thyroid cancer and that the incidence of thyroid cancer did not increase in patients with T1DM [36]. However, Carstensen et al. found that 3.3% of patients with T1DM had thyroid cancer, and women with T1DM had an increased risk of thyroid cancer [33]. In the present study, thyroid cancer was detected in 1.7% of the patients, which was consistent with the literature, and both patients were female. When a thyroid nodule is detected in female patients with T1DM, ultrasonographic features of the thyroid nodule should be carefully evaluated for thyroid cancer.

This study is limited by the cross-sectional single-center design. In addition, the study did not evaluate urinary iodine excretion. The most important feature that distinguishes this study from other studies is that it shows the effect of T1DM on thyroid morphology more clearly by excluding patients with thyroid disorders, including thyroid autoantibody positivity.

Conclusion

The thyroid morphology of patients with T1DM without thyroid disease was similar to that of healthy controls. Among patients with T1DM, the frequency of thyroid nodules was more frequent in patients with ICA positivity. Therefore, close follow-up of patients with ICA positivity in terms of thyroid nodules should be recommended. However, large, prospective, multicenter, and molecular-based studies are needed to more clearly evaluate the relationship between islet autoantibodies and thyroid morphology in patients with T1DM.

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Author contribution MC conceived the original idea, devised the project, designed the tables, analyzed the results, wrote the manuscript, and drafting of the manuscript. MES provided analysis and considerable intellectual input in the writing of the manuscript. IOU contributed to the discussion, reviewed and edited the manuscript. DS contributed to the discussion, reviewed and edited the manuscript. MT and HD contributed to the data collection. MO contributed to the discussion, reviewed and edited the manuscript. EC supervised all the procedures and manuscript preparation.

Declarations

Conflict of interest The authors declare no competing interests.

Ethics approval The study was approved by the ethics committee of our institute. This article does not contain any studies with animals performed by any of the authors (29.04.2019—62/16).

Informed consent Informed consent was obtained from all the study participants.

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ORIGINAL ARTICLE

A retrospective electronic medical record-based study of insulin usage and outcomes in insulin-naive Indian adults with T2DM: The REALITY study

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Abstract

Objective This retrospective longitudinal study analyzed the demographic profile, insulin usage pattern, and outcomes of insulin-naive adults with type 2 diabetes mellitus (T2DM) who initiated insulin glargine.

Methods The study included 1006 insulin naive T2DM individuals aged ≥ 18 years, treated with any insulin type between January 2016 and December 2018, using electronic medical records.

Results Majority of participants were men (55.8%) with a mean age of 59.8 ± 11.9 years and average T2DM duration of 12.0 ± 6.6 years. Insulin glargine was the most commonly used insulin (66.9%), followed by insulin aspart (16.4%), insulin degludec (15.1%), human insulin (11.1%), and insulin isophane (9.2%). At baseline, the mean glycated hemoglobin (HbA1c) was 8.9 ± 1.9%, mean fasting plasma glucose (FPG) was 190 ± 59 mg/dL, and mean post-prandial plasma glucose (PPG) was 264 ± 78 mg/dL. In the insulin glargine group, baseline HbA1c was 9.0 ± 1.7%, FPG was 196 ± 62 mg/dL, and PPG was 283 ± 81 mg/dL. Throughout the study, there was an improvement in HbA1c, FPG, and PPG levels in the insulin glargine group. Body weight remained relatively stable, and the number of hypoglycemic events was minimal and non-life-threatening.

Conclusion The REALITY study in India demonstrated that initiating basal insulin treatment in insulin-naive individuals with T2DM led to improved glycemic parameters over a 12-month period.

Keywords Glycemic control · Hypoglycemia · Insulin glargine · Type 2 diabetes mellitus · Real world evidence · India

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Introduction

The global burden of diabetes is steadily increasing, owing primarily to increased sedentary behavior, an overweight/obese population, and unhealthy lifestyles. Diabetes is rapidly increasing in low- and middle-income countries [1]. According to International Diabetes Federation (IDF) 2022, 8.3% of Indian population is estimated to have diabetes [2].

Type 2 diabetes (T2DM) is characterized by worsening hyperglycemia due to a progressive decline in pancreatic β-cells function and a deficit of β-cell mass. Uncontrolled diabetes is associated with the risk of vascular diseases, and long term macrovascular and microvascular complications [3]. Because of the progressive nature, a timely treatment strategy is, therefore, necessary to achieve and maintain optimal glycemic control early in the course of disease. Oral antidiabetic drugs (OADs) are the mainstay of therapy though limited in their ability to maintain glycemic control in long-term use [4]. Initiation of insulin therapy is required when lifestyle modifications combined with OADs fail to achieve metabolic control [5]. There is increasing support for the early initiation of insulin in people with T2DM to ensure target glycemic control and avoid microvascular and macrovascular complications [3]. Basal insulin secretion is essential for maintaining fasting plasma glucose (FPG) levels, primarily by inhibiting excessive glucose output from the liver [4]. Insulin glargine is the first long-acting insulin analogue that provides a more convenient replacement of physiological basal insulin compared to older long-acting insulin formulations [6]. Insulin glargine is thought to provide a more even distribution of insulin throughout the day, help achieve target glycemic control with once daily injection, and reduce the risk of hypoglycemia [7].

There is limited information available on the clinical management of people with T2DM in India, who were started on insulin glargine after failure of OADs. Therefore, the REALITY study was planned to explore the demographic profile, insulin usage patterns and outcomes in insulin-naïve participants with T2DM.

Materials and methods

This multicentric, non-interventional, retrospective, electronic medical record (EMR)-based study was conducted to explore the real-world insulin usage patterns and their longitudinal outcomes in insulin-naïve participants with T2DM. In the study, a total of 1006 insulin naive T2DM participants of ≥ 18 years age, who were initiated on insulin during the index period of January 01, 2016, to December 31, 2018, were enrolled. People with T1DM, T2DM of < 5 years duration, gestational diabetes, secondary diabetes (e.g., fibro calculus pancreatic diabetes), cancer, end-stage liver disease, end-stage renal failure, treatment with short-term insulin therapy (< 1 month) and those using other investigational drugs concurrently, were excluded from the study.

Analyses were performed using version 9.4 of SAS statistical software (SAS Institute Inc., Cary, NC, USA). Descriptive analyses were reported as mean, standard deviation (SD), minimum (min), maximum (max), median, interquartile range (IQR), percentages, and frequency count (n) for each evaluable parameter. The categorical variables were summarized using the frequency count (n) and percentage (%) for each possible value. The level of significance for statistical tests was 0.05 two-sided. *p*-values for statistical tests were provided with 4 decimals, or as < 0.0001.

Insulin outcome evaluation

At baseline, demographic, anthropometric and clinical characteristics including glycated hemoglobin (HbA1c), FPG, postprandial plasma glucose (PPG), anti-diabetic medications, co-morbidities prior to insulin initiation were abstracted from participants' medical records. Data on the insulin usage pattern (dose and type of insulin, frequency of administration), mean / median changes in insulin dose and outcome parameters for HbA1c, FPG, PPG, body weight and the incidence of hypoglycemia were collected from EMRs at 3, 6, and 12 months after initiation of insulin therapy. The mean / median change in the HbA1c levels was reported at 6 months and 12 months post-initiation of insulin glargine. The prescription patterns of OADs post initiation of insulin were also assessed at 3, 6 and 12 months. Details on study schedule are provided in Fig. 1.

Results

The study included 1006 participants with T2DM (55.8% [*n* = 561] men) having a mean age of 59.8 ± 11.8 years and an average T2DM duration of 12.0 ± 6.6 years. The mean height of the participants was 162.4 ± 98.8 cm, weight was 70.8 ± 12.8 kg, and BMI was 26.9 ± 4.7 kg/cm^2. The baseline systolic blood pressure was 128 ± 15 mmHg and diastolic blood pressure was 78 ± 9 mmHg. The most noted comorbidities were hypertension in 50.9% (*n* = 512), dyslipidemia in 28.8% (*n* = 290), hypothyroidism in 9.6% (*n* = 97), and coronary artery disease in 4.1% (*n* = 41) participants. Additional baseline characteristics of insulin-naïve participants with T2DM are presented in Table 1.

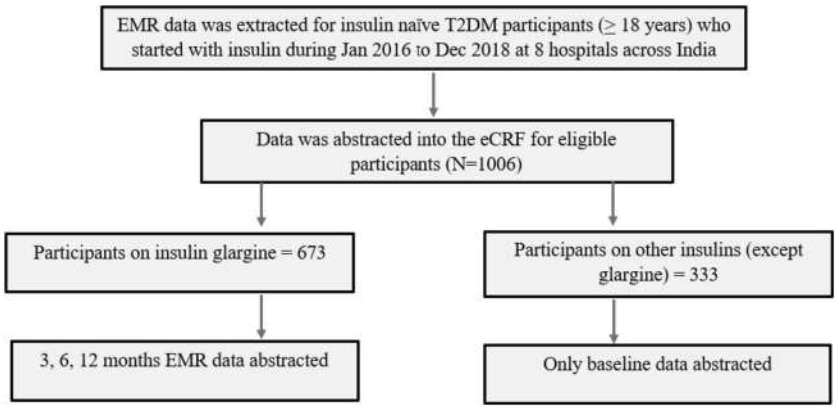

Fig. 1 Study flow chart. Abbreviations: T2DM – Type 2 Diabetes Mellitus; eCRF – Electronic Case Report Form; EMR – Electronic Medical Records

Table 1 Baseline characteristics of study participants

Characteristic		Value
Age (years) ($N=1006$)	Mean ± SD	59.8 ± 11.8
	Median (IQR)	61 (53, 68)
Subgroups; (n, %)	≥ 18–29	11 (1.1)
	≥ 30–49	171 (17.0)
	≥ 50–59	256 (25.4)
	≥ More than 60	568 (56.5)
BMI (kg/m^2) ($N=1000$)	Mean ± SD	26.9 ± 4.7
	Median (IQR)	26 (24, 29)
Subgroups; (n, %)	< 25	328 (32.6)
	25–35	613 (60.9)
	> 35	59 (5.9)
Duration of diabetes (years) ($N=1006$)	Mean ± SD	12.0 ± 6.6
	Median (IQR)	10 (7, 15)
Subgroups; (n, %)	= 5	24 (2.4)
	> 5 to ≤ 10	543 (54.0)
	> 10 to ≤ 20	322 (32.0)
	> 20	117 (11.6)

T2DM Type 2 Diabetes Mellitus; *BMI* Body mass index; *IQR* Interquartile range; *SD* Standard deviation

Glycemic parameters at baseline

Overall, the HbA1c value was recorded for 76.1% ($n=766$) participants with a mean of 8.9 ± 1.9%. The FPG of > 130 mg/dL was reported for 55.6% ($n=559$) participants with a mean of 201 ± 54 mg/dL. While 5.5% ($n=55$) participants reported > 180 mg/dL PPG with a mean of 276 ± 72 mg/dL.

In the insulin glargine group (U100 and U300; $n=673$), the mean HbA1c was 9.0 ± 1.7%; of these 63.7% (n = 429) participants had HbA1c ≥ 7%. The FPG of ≥ 130 mg/dL was reported for 44.5% (n = 300) participants with a mean of 209 ± 55 mg/dL. While PPG of ≥ 180 mg/dL was reported for 42.5% ($n=286$) participants with a mean of 298 ± 71 mg/dL.

Glycemic parameters of the overall population and the insulin glargine group at various study intervals are presented in Table 2.

Insulin usage pattern at baseline

At the onset (baseline), 66.9% ($n=673$) participants were on insulin glargine; 34.1% ($n=343$) on U100 (insulin glargine 100 IU per mL [Gla-100]) and 24.8% ($n=249$) on U300 (insulin glargine 300 IU per mL [Gla-300]). Information on the type of insulin glargine was unavailable for 8.1% ($n=81$) participants.

Other major types of insulin noted were insulin degludec in 15.1% ($n=152$), human insulin in 11.1% ($n=112$), and insulin isophane in 9.2% ($n=93$) participants. Among other categories of insulin (ultra-short/fast-acting), insulin lispro was noted in 4.1% ($n=41$) and insulin glulisine in 0.6% ($n=6$) participants. Short-acting, insulin aspart was noted in 16.4% ($n=165$), regular insulin in 7.4% ($n=74$), and intermediate-acting insulin isophane in 9.2% ($n=93$) participants. A combination of fast and intermediate-acting, insulin aspart protamine and insulin lispro protamine was noted in 1.8% ($n=18$) and 1.7% ($n=17$) participants, respectively.

The median (IQR) dose of insulin glargine (Gla-100, $n=343$; Gla-300, $n=249$; Gla-unclassified, $n=81$) was 14.0 (10, 20) IU; and it was most frequently administered at bedtime (58.2%; $n=392$) and once daily (39.2%; $n=26$). The median dose of insulin aspart, insulin degludec and human insulin was 16.0 IU, 15.0 IU, and 20.0 IU, respectively. Insulin aspart and insulin degludec were taken once daily by most participants and human insulin was taken twice daily.

Information on insulin usage pattern (including dose and frequency) at baseline is provided in Table 3.

Insulin glargine group assessment at 3, 6 and 12 months

Based on the records/data available, the use and change in dose of insulin glargine was noted for 24.7% ($n=166$),

Table 2 Glycemic parameters (HbA1C, FPG, PPG) at baseline and at different study intervals

Glycemic Parameters	Overall study population ($N=1006$), n (%)				Insulin glargine subset ($N=673$), n (%)			
	Baseline	3 months	6 months	12 months	Baseline	3 months	6 months	12 months
Glycated hemoglobin (HbA1c%), n (%)								
< 7	99 (9.8)	-	120 (11.9)	33 (3.3)	50 (7.4)	-	57 (8.4)	23 (3.4)
≥ 7	667 (66.3)	-	494 (49.1)	213 (21.2)	429 (63.7)	-	297 (44.1)	138 (20.5)
NA	240 (23.9)	-	365 (36.3)	388 (38.6	194 (28.8)	-	319 (47.3)	512 (76.0)
Fasting plasma glucose (FPG; mg/dL), n (%)								
< 80	4 (0.4)	12 (1.2)	10 (1)	6 (0.6)	3 (0.4)	6 (0.8)	8 (1.1)	5 (0.7)
80–130	72 (7.2)	128 (12.7)	177 (17.6)	87 (8.6)	42 (6.2)	77 (11.4)	124 (18.4)	56 (8.3)
> 130	559 (55.6)	188 (18.7)	384 (38.2)	148 (14.7)	300 (44.5)	105 (15.6)	174 (25.8)	98 (14.5)
NA	371 (36.9)	385 (38.3)	408 (40.6)	393 (39.1)	328 (48.7)	485 (72.0)	367 (54.5)	514 (76.3)
Postprandial plasma glucose (PPG; mg/dL), n (%)								
≤ 180	542 (53.9)	190 (18.9)	398 (39.6)	150 (14.9)	33 (4.9)	57 (8.4)	70 (10.4)	41 (6.0)
> 180	55 (5.5)	112 (11.1)	139 (13.8)	72 (7.2)	286 (42.4)	114 (16.9)	207 (30.7)	108 (16.0)
NA	409 (40.7)	411 (40.9)	442 (43.9)	412 (41)	354 (52.6)	502 (74.5)	396 (58.8)	524 (77.8)

T2DM Type 2 Diabetes Mellitus; *NA* Not available

32.4% ($n=218$) and 21.8% ($n=147$) participants at 3, 6 and 12 months, respectively. The median (IQR) change in dose of insulin glargine from baseline to 3, 6 and 12 months was 4.0 IU (2, 6), 4.0 IU (1, 6), and 8.0 IU (4, 12), respectively (Table 4). For the insulin glargine group, an improvement in HbA1c, FPG, and PPG levels was indicated during the study. The change in body weight was minimal throughout the study (Table 5).

Hypoglycemic events in the insulin glargine subset

At 3 months, a total of 43 hypoglycemic events (38 mild, 4 moderate, and 1 severe) were noted in 39 participants of insulin glargine subset ($N=673$). None of events were life-threatening or required hospitalization. The severe hypoglycemic event was serious in nature reported with antidiabetic medications: metformin, glimepiride, vildagliptin, canagliflozin and insulin glargine U100. Hypoglycemia was possibly related to antidiabetic therapy in 36 events and not related in 7 events. Forty hypoglycemic events were resolved, 1 recovered with sequelae and status of 2 events was unknown.

At 6 months, 58 hypoglycemic events (47 mild, and 11 moderate) were noted in 45 participants of insulin glargine subset ($N=673$). Thirty-seven events were possibly related to antidiabetic medication, 1 unlikely and 20 were not related. Fifty-six events were resolved, and the status of the 2 events was unknown.

At 12 months, a total of 36 hypoglycemic events (32 mild, and 4 moderate) were reported in 26 participants of insulin glargine subset ($N=673$). Twenty-seven events were possibly related to antidiabetic medication, 1 unlikely and 8 were not related. Thirty-two events were resolved, and the status of 4 events was unknown.

Oral antidiabetic drugs usage throughout the study

Prior to insulin initiation, 63.4% ($n=638$), 45.8% ($n=461$) and 35.7% ($n=359$) participants were taking at least one, two, or three OADs, respectively. The most noted OADs were biguanides (60.5%; $n=609$), sulfonylureas (41.1%; $n=413$), and dipeptidyl peptidase-4 inhibitors (36.1%; $n=363$). As per the records, the usage patterns remained almost same across different time points with biguanides, sulfonylureas, and dipeptidyl peptidase-4 inhibitors as the most common OADs.

Missing values

Since it was a retrospective EMR-based study, all the required information was not available in the medical records, and no imputations were made for missing values.

Discussion

This multicentric retrospective study evaluated the demographic profile of insulin-naïve T2DM Indian participants initiated on insulin in a larger cohort. In addition, the study assessed the insulin usage pattern, the glycemic parameters, and incidences of hypoglycemia. Most participants were initiated with insulin glargine and improvement in glycemic parameters was indicated over 12 months.

In our study, the mean age of T2DM participants was comparable with other Asian population-based real-world

Table 3 Insulin usage pattern and frequency at baseline ($N=1006$)

Insulin		Gla-100	Gla-300	Gla Unclassified	Insulin lispro	Insulin aspart*	Insulin glulisine	Regular insulin	Insulin isophane	Insulin aspart protamine	Insulin lispro protamine	Insulin degludec	Human insulin
Dose; IU/mL	n (%)	343 (34.1)	249 (24.8)	81 (8.1)	41 (4.1)	164 (16.3)	6 (0.6)	74 (7.4)	93 (9.2)	18 (1.8)	17 (1.7)	151 (15.1)	112 (11.1)
	Mean (SD)	23.0 (12.8)	11.7 (4.2)	14.5 (7.7)	22.8 (18.3)	19.0 (10.1)	25.5 (13.3)	16.4 (5.1)	24.3 (13.2)	15.3 (6.9)	16.3 (8.1)	16.6 (7.7)	23.6 (12.7)
	Median	20	10	12	16	16	22	15	20	13	16	15	20
	IQR	14, 30	10, 12	10, 16	8, 22	12, 30	9, 38	10, 20	10, 32	10, 22	8, 12	10, 20	10, 30
Frequency, n (%)	BID	2 (0.6)	-	3 (3.7)	12 (29.3)	31 (18.8)	1 (16.7)	40 (55.6)	60 (64.5)	1 (5.6)	10 (58.8)	27 (17.8)	62 (55.4)
	HS	290 (84.3)	60 (24.1)	42 (51.9)	1 (2.4)	2 (1.2)	-	1 (1.4)	-	1 (5.6)	1 (5.9)	29 (19.1)	-
	PRN	1 (0.3)	-	-	-	-	-	-	-	-	-	-	-
	QAM	2 (0.6)	5 (2.0)	1 (1.2)	1 (2.4)	4 (2.4)	-	-	3 (3.2)	2 (11.1)	1 (5.9)	1 (0.7)	3 (2.7)
	Once in afternoon	-	2 (0.8)	1 (1.2)	-	-	-	-	-	-	-	-	-
	QD	49 (14.2)	182 (73.1)	34 (42.0)	7 (17.1)	87 (52.7)	-	27 (37.5)	28 (30.1)	14 (77.8)	5 (29.4)	92 (60.5)	37 (33.0)
	TID	-	-	-	20 (48.8)	40 (24.2)	5 (83.3)	6 (8.3)	2 (2.2)	-	-	2 (1.3)	10 (8.9)

*Participants initiated on insulin aspart, dose was reported for 164 out of 165 participants

T2DM Type 2 Diabetes Mellitus; *SD* Standard deviation; *IQR* Interquartile range; *BID* Bis in die (twice a day); *HS* Hora somni (at bedtime); *PRN* Pro re nata (at needed); *QAM* Quaque ante meridiem (once in morning); *QPM* Quaque post meridiem (once in afternoon); *QD* Quaque die (once daily); *TID* Ter in die (three times a day)

Table 4 Change in insulin glargine dose at 3, 6 and 12 months

Insulin glargine dose		3 months	6 months	12 months
n		166	218	147
Change from baseline (IU)	Mean ± SD	4.9 ± 6.6 ($p < 0.0001$)	4.7 ± 7.7 ($p < 0.0001$)	8.0 ± 8.3 ($p < 0.0001$)
	Median	4.0	4.0	8.0
	IQR	2, 6	1, 6	4, 12

IQR Interquartile range; *SD* Standard deviation; *IU* International unit

Table 5 Change in glycemic parameters and body weight in participants on insulin glargine

Parameter			3 months	6 months	12 months
HbA1c, %	*n*		-	316	128
	Change from baseline	Mean ± SD (p value)	-	-0.7 ± 1.5 ($p < 0.0001$)	-0.9 ± 1.8 ($p < 0.0001$)
		Median	-	0.0	-0.7
		IQR	-	-1.5, 0.0	-1.9, 0.0
FPG, mg/dL	*n*		169	279	131
	Change from baseline	Mean ± SD (p value)	-50 ± 72 ($p < 0.0001$)	-46 ± 73 ($p < 0.0001$)	-47 ± 74 ($p < 0.0001$)
		Median	-50.0	-39.0	-36.0
		IQR	-90.0, -3.0	-93.0, 0.0	-84.2, 0.0
PPG, mg/dL	*n*		149	252	129
	Change from baseline	Mean ± SD (p value)	-65 ± 103 ($p < 0.0001$)	-49 ± 92 ($p < 0.0001$)	-61 ± 88 ($p < 0.0001$)
		Median	-59.0	-45.0	-55.0
		IQR	-108.0, -8.0	-112.0, -8.0	-124.0, -1.0
Body weight (kg)	*n*		519	654	500
	Change from baseline	Mean ± SD (p value)	0.2 ± 2.6 (0.2025)	0.3 ± 2.9 (0.0049)	0.3 ± 2.9 (0.0200)
		Median	0.0	0.0	0.0
		IQR	0.0, 0.2	00, 0.9	0.0, 0.5

HbA1c Glycated hemoglobin; *FPG* Fasting plasma glucose; *PPG* Postprandial plasma glucose; *IQR* Interquartile range; *SD* Standard deviation

studies [8]. We noted that, 66% individuals of the total enrolled population were obese (BMI ≥ 25 kg/m^2). A cross-sectional registry-based retrospective study in India noted that 46.4% of the participants were obese and were younger (54.6 ± 11.0 years) compared to our study population [9].

In our study, most insulin-naïve participants had at least one comorbid condition, commonly hypertension (50.9%) and/or dyslipidemia (28.8%). Other studies in India also show a higher prevalence of vascular and lipid metabolic disorders in people with diabetes [10–12]. As per American Diabetes Association (ADA), hypertension and dyslipidemia are among the top 15 comorbid conditions commonly observed in people with T2DM [13].

The Indian Council of Medical Research (ICMR) and Research Society for the Study of Diabetes in India (RSSDI) guidelines recommend the use of insulin in people with T2DM having HbA1c > 9% [14]. In this study HbA1c at baseline was 8.9 ± 1.9% which is high and, about 67% of participants at baseline were taking insulin glargine, which is considered safer in terms of reducing the risk of hypoglycemia, compared to short-acting insulin. Basal insulin was chosen in accordance with available literature and RSSDI recommendations [15].

The mean FPG noted at baseline in our study is similar to that reported in an Asian population-based study [10]. While PPG noted in our study was higher and HbA1c levels were on the lower side compared to another Indian population-based study [16]. Among all the components present in an individual's diet, carbohydrates exert the most significant impact on blood glucose levels. The quantity and type of carbohydrates consumed are pivotal factors influencing postprandial glucose levels. The prevalence of high carbohydrate intake within the population may be a contributing factor to elevated postprandial glucose levels [17].

In the insulin glargine group of our study, there was an improvement in the HbA1c, FPG and PPG levels throughout

the study duration. ATOS, a multi-country, real-world study assessed the effectiveness and safety of insulin glargine 300 U/mL in insulin-naïve people with T2DM. The ATOS study reports a reduction in HbA1c by − 1.5% and − 1.9%, at 6 and 12 months, respectively [10]. FPG was also reduced by − 3.4 mmol/L and − 3.9 mmol/L at 6 and 12 months, respectively. Higher levels of HbA1c and FPG reduction seen in the ATOS study may be associated with higher baseline values of HbA1c and FPG compared to our study [10].

The weight change was minimal throughout our study (3, 6 and 12 months), which is supported by another real-world study conducted in wider geographic regions (Asia, the Middle East, North Africa, Latin America, and Eastern Europe) [10]. However, a study based on post-hoc analysis of 16 clinical trials where insulin therapy was initiated with the OADs, reported a substantial increase in body weight in Asian compared to non-Asian subjects [18].

In our study, a total of 43 hypoglycemic events were reported at 3 months, 58 events reported at 6 months, and 36 events reported at 12 months. The hypoglycemic events reported in our study are comparable to the real-world ATOS study [10].

We note that biguanides (60.5%), sulfonylureas (40.1%), and dipeptidyl peptidase-4 (DPP-4) inhibitors (36.1%) were the most used OADs. Similarly in ATOS, biguanides were the most used OAD at baseline (88.9%), followed by sulfonylureas (73.0%) and DPP-4 inhibitors (43.5%). Our findings are consistent with the pattern of treatment followed in India.

This study provides real-world data on the insulin usage patterns and the outcomes in Indian people with T2DM. A major limitation of the study was its retrospective nature and the dependency on secondary data source through EMRs. Therefore, there were challenges of computing missing data, including loss to follow-up at various stages of the study. Additionally, because of the EMR-based study design, the incidences of hypoglycemia may have been under-reported. There could also be a potential center selection bias. Another challenge was missing data on insulin education of patients, their compliance, storage, site, technique of administration and information on dietary survey. The scope and nature of the present research did not focus on the biochemical parameters and its significance in capturing the outcomes of insulin usage. Hence, further, large, and complete dataset studies would be required to validate our study findings.

Conclusion

In this EMR-based REALITY study, focusing on insulin-naïve participants with T2DM in India, most individuals were initially prescribed insulin glargine. The results highlighted a noteworthy improvement in glycemic parameters over a 12-month period. The study identified hypertension and dyslipidemia as the most prevalent comorbid conditions, while biguanide and sulfonylurea emerged as the most preferred concomitant antidiabetic medications. Furthermore, the changes in body weight and the occurrence of hypoglycemic events were found to be comparable to similar real-world studies.

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Authors' Contributions All authors adhered to the ICMJE authorship criteria.

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Writing (review & editing)- A Gadekar.

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Data Availability Qualified researchers may request access to patient-level data and related documents [including, e.g., the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications]. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at https://vivli.org/.

Declarations

Ethics statement Ethical approval for the study was obtained from the local ethics committee.

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Conflicts of interest Authors declare no conflict of interests.

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ORIGINAL ARTICLE

Prevalence and associated factors of tenia pedis among patients with diabetes in Jordan

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Abstract

Background Diabetes mellitus is an etiological factor of tinea pedis (TP) which can increase the risk of diabetes-related foot complications. There is scarce research investigating the epidemiology of TP among patients with diabetes and this study contributed to filling this gap.

Objective To identify the prevalence and the associated factors of TP among patients with diabetes in Jordan.

Methods A total of 375 patients with diabetes were recruited in a cross-sectional study at the National Centre for Diabetes, Endocrinology and Genetics in Amman, Jordan. TP was examined by a specimen culture and microscopic study. Several independent variables were collected, including sociodemographic, clinical, and foot self-care variables. Multivariant logistic regression was conducted to test independent factors associated with the prevalence of TP.

Results Positive TP was present in 211 participants with a prevalence of 56.3%. Multiple logistic regression resulted in four significant associated factors; being highly educated ($\beta = 1.69$, $p = 0.03$), presence of onychomycosis ($\beta = 4.48$, $p < 0.01$), wearing socks as a daily habit ($\beta = 2.30$, $p < 0.01$), and frequency of feet washing (1–2 times\day) ($\beta = 2.54$, $p = 0.04$).

Conclusion Patients with diabetes in Jordan have a high prevalence of TP. Factors including educational level, onychomycosis infection, and self-care activities (i.e., socks wearing habits and foot hygiene) were found to be associated with the prevalence of TP.

Keywords Tinea pedis · Diabetes mellitus · Prevalence · Diabetic foot · Jordan

Introduction

Diabetes is a serious chronic condition that increases the risk of diabetes-related foot disease and is a main cause of amputation and disability [1]. The prevalence of diabetes-related foot amputations among hospitalised patients varied between 1.4 and 5.8 [2]. In Jordan, previous research reported a high prevalence of diabetes-related foot complications including diabetes-related foot ulcers (DFUs), foot deformities, onychomycosis, amputations, and peripheral vascular disease [3–6].

Diabetes-related immune dysfunction can be responsible for developing diabetes-related foot infections [7], and these are associated with high costs, frequent hospitalisations, and high mortality [8]. Tinea pedis (TP) is one of the common foot fungal infections that primarily affects the foot skin, particularly inter-digital web spaces and the plantar surface of the foot [9]. These superficial infections may impose cosmetic problems on patients as well as an increase in the risk

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for secondary bacterial infections such as lower limb cellulitis [10]. TP affects normal populations, but it was reported to be higher in people with diabetes [11, 12]. Furthermore, the presence of TP in patients with diabetes was significantly associated with DFUs [13–16]. Therefore, investigating TP among patients with diabetes including testing the associated factors appears essential to guide health strategies and clinical interventions to prevent TP and subsequently reduce the risk of diabetes-related foot complications.

We conducted a systematic search to identify the studies that investigated the prevalence of TP and its associated factors among patients with diabetes (Supplementary file 1). We noticed that there is limited epidemiological research globally. Only four studies assessed the prevalence of TP among people with diabetes which varied between 14.2% and 42.5%. Our search results also showed no previous studies from Jordan that had investigated the prevalence of TP among patients with diabetes. Thus, the current study is committed to contributing to this area of research.

Materials and methods

Study design

Secondary data from a cross-sectional study was used to investigate the prevalence of toenail onychomycosis and its associated factors among patients with diabetes in Jordan [6]. The study sample size was calculated in the original research and included 375 patients with diabetes who visited diabetes clinics (excluding the diabetic foot clinic) at the National Centre for Diabetes, Endocrinology and Genetics (NCDEG) (Amman-Jordan) in the period from 1st of November 2016 to 28th of February 2017 [6]. The included participants were adults (above 18 years old) who had type 1 or type 2 diabetes. Participants who had received antifungal medications or ointments during the last three months were excluded [6].

Data collection procedure

This study was approved by the institutional review board (IRB) committee at the NCDEG for ethical approval (Decision No.1/2016). The study was then advertised in the research setting and the selected participants signed a consent form after having a substantial understanding of the study's aim and procedure. Participants were then interviewed to collect socio-demographic information and to assess foot self-care practices using a self-reported questionnaire. In addition, medical records were reviewed to collect medical history and clinical variables. The second author (H.A), who is a licensed medical doctor and trained podiatrist, collected the study data at the NCDEG.

Variables collected

The collected variables included socio-demographics, a study questionnaire, and health information. The socio-demographics included age, gender, total family income (in Jordanian Dinar (JD)), occupation (employed full-time, employed part-time, unemployed, or retired), marital status (single, married, divorced, or widowed), level of education (uneducated, primary school, high school, bachelor, or postgraduate), and smoking status (none, current, or past smoker). The definitions of all these variables are outlined in detail elsewhere [6].

The study questionnaire included eight items that investigated the frequency of foot self-care practices including daily foot washes, use of antibiotics (last year or current), foot screening and follow-up by a podiatrist (once, more than once/year, or never), type of footwear (sandal or shoes), the habit of using footwear (none, <8 h, or >8 h /day), and the habit of wearing socks (yes, no) [6].

The health information included type of diabetes (type 1 or type 2), duration of diabetes (in years), treatment of diabetes (diet, oral hypoglycemics drugs (OHD), insulin, or OHD and insulin), glycosylated haemoglobin (HbA1C $<7\%$ is controlled and HbA1C $\geq 7\%$ is uncontrolled) [17], body mass index (BMI), comorbidities (medical reports of hypertension, dyslipidaemia, nephropathy, cardiovascular disease, or retinopathy), sensory neuropathy (two incorrect answers out of three applications of 10-g Nylon Semmes–Weinstein monofilament) [18], and foot deformities (clinical inspection of the bunion, pes planus, pes cavus, Charcot, hummer or claw toes [4]. The definitions of all these variables are outlined in detail elsewhere [6].

Outcome of interest

TP was defined as a fungal infection of the skin of the foot particularly the web spaces of the toes or less common in the plantar of the foot [10]. In our study, a specimen was obtained from the lateral fourth web space and any suspected areas in the skin of the foot (i.e., itching, scaling, redness, or blistering) using a scalpel blade. The collected specimens were sent to cultivation (two days at 30 °C), and then the culture was considered negative if the direct microscopic examination revealed no growth after four weeks of incubation [19].

Statistical analysis

The IBM SPSS software (V20) was used for data analysis. Frequencies and proportions were used for descriptive statistics while chi-square test was used to examine the correlations between categorical variables. Multivariant logistic

Table 1 Descriptive characteristics of the study population

Variables	(n)	(%)
Body mass index (BMI) (kg/ m^2):		
Normal	44	11.8%
Overweight	119	31.7%
Obese	212	55.5%
Duration of diabetes (year):		
< 5	75	20.0%
5–10	102	27.2%
≥ 10	198	52.8%
Type of DM:		
Type 1	12	3.2%
Type 2	363	96.8%
Type of DM treatment:		
Insulin	45	12.0%
OHD	136	36.3%
Insulin and OHD	194	51.7%
HbA1c:		
Controlled	114	30.4%
Uncontrolled	261	69.6%
Hypertension:		
Yes	309	82.4%
No	66	17.6%
Dyslipidemia:		
Yes	318	84.4%
No	57	15.6%
Nephropathy:		
Yes	54	14.4%
No	321	85.6%
Cardiovascular disease:		
Yes	157	41.9%
No	218	48.1%
Retinopathy:		
Yes	198	52.8%
No	177	47.2%
Neuropathy:		
Yes	164	43.7%
No	211	56.3%
Foot deformity:		
Yes	75 300	20.0%
No		80.0%
Frequency of foot washing:		
3–5 times per day	226	60.3%
1–2 times per day	113	30.1%
Less than 7 times per week	36	9.6%
Current use of antibiotics:		
Yes	111	29.6%
No	264	70.4%
Antibiotics usage in the past year:		
Once or non	111	29.6%
2–4 times yearly	194	54.7%
More than 4 times yearly	70	18.7%
Type of footwear:		
Sandals	187	49.9%
Shoes	188	50.1%
Footwear wearing habit:		
Non	20	5.3%
Less than 8 h/ day	291	77.6%
More than 8 h/day	64	17.1%
Wearing socks as a daily habit:		
Yes	307	81.9%
No	68	18.1%

regression was conducted to eliminate confounders and to identify the relationships (beta coefficient). The *p*-value in this study was set at < 0.05.

Results

The sociodemographic and health characteristics of the study participants ($n = 375$) in addition to the results of the foot self-care questionnaire are presented in Table 1.

The prevalence of TP based on 211 positive specimens was 56.3%. Table 2 shows the different types of mycosis that were found in this study including their frequencies.

The bivariate analysis (chi-square test) showed significant associations ($p < 0.05$) between the prevalence of TP and type of diabetes, level of education, frequency of feet washing, socks wearing as a daily habit, frequency of using antibiotics in the past year, and foot deformity (Table 3).

The final multiple logistic regression showed that the prevalence of TP was significantly associated with being highly educated, the presence of onychomycosis, wearing

Table 2 Types of mycosis and their frequencies

Mycoses type	(n)	(%)
Trichophyton spp. (dermatophyte)	62	16%
Epidermophyton (dermatophyte)	2	0.5%
Candida.glaberta (yeast)	52	13.9%
Rhod.rapra (yeast)	4	1.1%
Candida.krusei (yeast)	14	3.7%
Trichosporon Beigelii (yeast)	14	3.7%
Cryptococcus terreus (yeast)	1	0.3%
Penicillin, spp. (NDM)	71	18.9%
Aspergillus.spp.(NDM)	23	6.1%
Cladosporium (NDM)	14	3.7%
Aletrnaria (NDM)	13	3.5%
Aspergillus. Niger (NDM)	5	1.3%
Rhizopus (NDM)	2	0.5%
Scopulariopsis (NDM)	0	0.0%

Table 3 Factors associated with TP among study participants including bivariate testing and Beta coefficients

Variables	TP absent $N=164$	TP present $N=211$	p-value (x^2 test)	Beta Coefficients	p-value
Age group (year)					
< 40	11 (2.9%)	10 (2.6%)	0.64		
40- 59	74 (19.7%)	102 (27.2%)			
≥ 60	79 (21%)	99 (26.4%)			
Gender					
Male	96 (25.6%)	116 (0.9%)	0.27		
Female	68 (18.1%)	95 (25.3%)			
Marital status					
Single (divorced or widowed)	33 (8.8%)	48 (12.8%)	0.66		
Married	131 (34.9%)	163 (43.4%)			
Employment status					
Unemployed	69 (18.4%)	75 (2%)	0.34		
Employed	47 (12.5%)	61 (16.2%)			
Retired	48 (12.8%)	75 (2%)			
Level of education					
High school or less or illiterate	89 (23.7%)	93 (24.8%)	0.03	1	
More than high school	75 (2%)	118 (31.4%)		1.69	0.03
Smoking status					
Current smoker	48 (12.8%)	42 (37.8%)	0.10		
Non-smoker	98 (26.1%)	142 (37.8%)			
Ex-smoker	18 (4.8%)	27 (7.2%)			
Body mass index (BMI) (kg/ m^2)					
Normal	23 (6.2%)	21 (5.6%)	0.33		
Overweight	47 (12.5%)	72 (19.2%)			
Obese	94 (25%)	118 (31.4%)			
Duration of diabetes (year)					
< 5	30 (8%)	45 (12%)	0.62		
5–10	43 (11.4%)	59 (15.7%)			
≥ 10	91 (24.2%)	107 (28.5%)			
Type of DM					
Type 1	9 (2.4%)	3 (0.8%)	0.02		
Type 2	155 (41.3%)	208 (55.4%)			
Type of DM treatment					
Insulin	23 (6.1%)	22 (5.8%)	0.51		
OHD	60 (16%)	76 (20.2)			
Insulin and OHD	81(21.6%)	113 (30.1%)			
HbA1c (%)					
Controlled	46 (12.2%)	68 (18.1%)	0.22		
Uncontrolled	118 (31.6%)	143 (38.1%)			
Hypertension					
No	29 (7.7%)	36 (9.6%)	0.49		
Yes	135 (36%)	175 (46.6%)			
Dyslipidemia					
No	28 (7.4%)	26 (6.9%)	0.12		
Yes	136 (36.2%)	185 (49.3%)			
Nephropathy					
No	135 (18%)	186 (24.8%)	0.07		
Yes	29 (7.7%)	25 (6.6%)			

Table 3 (continued)

Variables	TP absent $N=164$	TP present $N=211$	p-value (x^2 test)	Beta Coefficients	p-value
Cardiovascular disease					
No	93 (24.8%)	125 (33.3%)	0.34		
Yes	71 (18.9%)	86 (22.9%)			
Retinopathy					
No	72 (19.2%)	103 (27.4%)	0.20		
Yes	92 (24.5%)	108 (28.8%)			
Frequency of foot washing					
Less than 7 times per week	23 (6.1%)	13 (3.4%)	0.02	1	
1–2 times \ day	43 (11.4%)	70 (18.6%)		2.54	0.04
More than 3 times per day	98 (26.1%)	128 (34.1%)		1.87	0.14
Current use of antibiotics					
No	115 (30.6%)	149 (39.7%)	0.50		
Yes	49 (13%)	62 (16.5%)			
Antibiotic usage in the past year					
Once or non	42 (11.2%)	69 (18.4%)	0.01		
2–4 times yearly	81 (21.6%)	113 (30.1%)			
More than 4 times yearly	41 (10.9%)	29 (7.7%)			
Type of footwear					
Sandals	76 (20.2%)	112 (29.8%)	0.11		
Shoes	88 (23.4%)	99 (26.4)			
Footwear wearing habit					
No	11 (2.9%)	9 (2.4%)	0.11		
Less than 8 h\ day	119 (31.7%)	172 (45.8%)			
More than 8 h\ day	34 (9%)	30 (8%)			
Wearing socks as a daily habit					
No	39 (10.4%)	29 (7.7%)	< 0.01	1	
Yes	125 (33.3%)	182 (48.5%)		2.30	< 0.01
Foot deformity					
No	120 (32%)	180 (48%)	< 0.01		
Yes	44 (11.7%)	31 (8.2%)			
Neuropathy					
No	91 (24.2%)	120 (32%)	0.43		
Yes	73 (19.4%)	91 (24.2%)			
Onychomycosis					
No	98 (26.1%)	61 (16.2%)	< 0.01	1	
Yes	66 (17.6%)	159 (42.2%		4.48	< 0.01

socks as a daily habit, and frequency of feet washing (1–2 times\day) (all $p < 0.05$) (Table 3).

Discussion

This study found a high prevalence of TP (56.3%) among patients with diabetes in Jordan which was significantly associated with the level of education (graduate level), presence of onychomycosis, wearing socks as a daily habit, and frequency of foot washing (1–2 times\day). The resulting prevalence of TP among patients with diabetes in Jordan is higher than the previous research in countries including Tukey, Korea, and the US (prevalence ranged 14.2–42.5%) [16, 20, 21]. It is possible that factors related to culture, geography, climate, environment, or genetics have led to this variation. However, this assumption emphasizes the need for more research to explore the aetiology behind this discrepancy.

We found that patients with a higher level of education (graduate level; diploma or higher) were 1.69 more likely to develop TP. This is a surprising finding which does not support the common hypothesis in diabetic foot care in which low knowledge or education can lead to poor foot self-care activities and more diabetic foot complications [22]. The

previous studies that investigated the associated factors with TP among patients with diabetes did not also find this association [16, 20, 21]. More interestingly is that our finding is in contrary to a large cohort study of 2761 participants from a normal (non-diabetic) population in which low education was associated with a higher prevalence of TP [23]. We assume that highly educated individuals in this study spend more time in office-related jobs wearing occlusive shoes with socks all that time, then probably increasing the chance of developing TP. We recommend clinicians consider educated people with diabetes the same as non-educated in terms of assessing dermatological fungal infections such as TP.

Our findings also showed that the presence of toenail onychomycosis was significantly associated with TP. Presence of secondary fungal infections such as onychomycosis is expected due to diabetes-related immune dysfunction [7]. Our finding is new in terms of the prevalence of TP among patients with diabetes but studies from the normal (non-diabetic) populations match our result and demonstrate that onychomycosis and TP are associated infections [24–26]. We recommend clinicians to check for TP when they notice onychomycosis.

We also noticed that patients who wore any type of socks as a daily routine were more likely to have TP compared to those who did not habitually wear socks. The same as the above discussion, this is a new association which was not found in the previous few studies of the prevalence of TP among patients with diabetes [16, 20, 21]. However, prevalence studies from the normal (non-diabetic) populations found socks and footwear habits to be associated with TP [27–29]. The occlusive environment of footwear and socks can create a humid environment that can be suitable for fungal growth [27, 28]. We recommend health education interventions for patients with diabetes to adopt socks and footwear that promote foot ventilation and to routinely check for any progression of TP.

Lastly, our results showed that patients who frequently wash their feet (1–2 times\day) had significantly higher odds of developing TP. This is expected as previous studies found associations between wet environments including foot washing and TP [26, 30, 31]. However, although our results also showed that the prevalence of onychomycosis was the highest among patients who wash their feet more than 3 times\day, the odd of developing TP among this group was not significant. Future research is needed to re-test the association between foot washing and the prevalence of onychomycosis. Clinicians may also need to educate patients with diabetes to dry the web space after each foot washing to reduce the risk of developing TP.

Strengths and limitations

The main strength of this study is using a large sample size to present the prevalence of TP among patients with diabetes in Jordan. Additionally, the detected TP cases were examined thoroughly using a specimen culture followed by a microscopic assessment. However, there are some limitations. First, this study was from a single center and there was no sampling from other diabetes centres in Jordan to be confident of a national presentation, but the research setting (NCDEG) is a well-known public diabetes centre in the capital of Jordan, and it receives patients from the whole country. Second, the implemented design is not optimal to identify causality. Third, the foot self-care questionnaire was used without formal validation, and it was self-reported by the study participants which might lack accuracy. These aforementioned limitations could make this study not exempt from having false negatives or positives during hypothesis testing. Thus, further future research is needed.

Conclusion

This study showed a high prevalence of TP among patients with diabetes in Jordan. Factors such as being highly educated, having toenail onychomycosis, the daily habit of wearing socks, and the habit of frequent foot washing were significantly associated with the prevalence of TP among the study population. We recommend considering these associated factors in routine practice through health education on the appropriate foot self-care practices to reduce the prevalence of TP among patients with DM.

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Declarations

Ethics approval and consent to participate Ethical approval was obtained from the IRB committee at the NCDEG and then the eligible participants were provided with an information sheet, and they signed a consent form.

Conflict of interest The authors declare no competing interests.

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ORIGINAL ARTICLE

Evaluation of HbA1c levels as probable diagnostic of depression symptoms in Mexican individuals with type 2 diabetes mellitus

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Abstract

Background Depression is present in individuals with type 2 diabetes mellitus.

Objective We evaluated the sociodemographic, anthropometric, and clinical features of Mexican individuals with clinical depressive symptoms in order to identify predictors for depression symptoms; finally, we evaluated if HbA1c levels could be used as a probable diagnostic of depressive symptoms in individuals with type 2 diabetes mellitus.

Methods The population studied consisted of 376 Mexicans with diabetes who were interviewed to collect information about comorbidities and habits. The evaluation of depressive symptoms was performed using the Hamilton scale. For a possible clinical association between HbA1c levels and depressive symptoms, we performed chi-square tests (χ^2)/ t tests. A multivariate logistic regression model with the backward conditional method was used to identify predictors of depressive symptoms. An ROC curve was plotted to assess the possible role of HbA1c as a diagnostic predictive test of depression symptoms.

Results A total of 42.8% ($n = 161$) individuals showed clinical depressive symptoms. When comparing individuals with and without depression symptoms, those with depression symptoms showed higher levels of glucose and HbA1c; additionally, gender ($p = 0.04$), age ($p = 0.006$), HbA1c ($p < 0.01$), and complications related to diabetes were predictive factors for clinical depressive symptoms ($p < 0.01$). However, HbA1c showed a low diagnostic accuracy for depressive symptoms, with an area under the ROC curve of 0.59.

Conclusions Our findings provided evidence of the sex, age, HbA1c levels, and medical complications as predictors of clinical depressive symptoms in individuals with diabetes mellitus. Nevertheless, HbA1c levels are not useful as a diagnostic instrument for depressive symptom severity in these Mexican individuals.

Keywords Diabetes · HbA1c · ROC curve · Mexican population · Depression

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Introduction

Type 2 diabetes mellitus is characterized by chronic hyperglycemia and defective metabolism of carbohydrates, lipids, and proteins caused by an inappropriate secretion and/or action of insulin [1]. According to the International Diabetes Federation, 537 million people have diabetes, and it is one of the greatest health issues of the twenty-first century [2]. Around 79% of individuals with diabetes live in low and middle income countries including Mexico, where the prevalence of diabetes is high (9.4%) [3].

Type 2 diabetes is related to several comorbidities, such as diabetic nephropathy, retinopathy, fatty liver, and ischemic heart disease [4]. Diabetes is also associated with several complications including mental health

related disorders particularly depressive disorders that can potentially reduce the quality of life in individuals with diabetes [5–7]. Depression itself is probably the most common mental disorder worldwide/in America, affecting more than 17% of the general population in the USA [8], and it has 20–60 higher odds in individuals with type 2 diabetes mellitus than their healthy counterparts [9].

Depression is a chronic disease that affects thoughts, mood, and physical health [10]. The main characteristics of depression include anhedonia and lack of interest; it could also be accompanied by weight change, sleep disturbances, or lack of energy among other characteristics [11]. The relationship between diabetes and depression has been described as bi-directional, as individuals with depression have an increased risk of developing diabetes, whereas individuals with diabetes are twice as likely to have significant clinical depressive symptoms when compared to non-diabetes individuals [12]. It has been described that factors such as poor glycemic control, bad eating habits, and lack of exercise adherence contribute to the development of clinical depression or worse symptom severity in people with diabetes [13].

Studies of individuals with type 2 diabetes and clinical depression, have reported higher concentrations of glycated hemoglobin (HbA1c) along with an important blood sugar imbalance [14, 15]. In the medical practice, it is not common to evaluate depressive symptom severity in individuals with diabetes; nevertheless, it is common to evaluate anthropometric measures and to request laboratory tests that include HbA1c. Therefore, the aims of the present study were: i) to compare demographic and clinical characteristics of individuals with type 2 diabetes mellitus with and without clinical depressive symptom, ii) to identify sociodemographic, anthropometric, and clinical predictors of clinical depressive symptom in individuals with type 2 diabetes mellitus, and iii) to determine the diagnostic accuracy of HbA1c concentrations for clinical depressive symptom in individuals with type 2 diabetes mellitus.

Material and methods

Study participants

Our study group comprised a total of 376 Mexican individuals, including men and women over 18 years of age, diagnosed with type 2 diabetes mellitus. They were identified at the diabetes clinic of the High Specialization Regional Hospital Dr. Gustavo A. Rovirosa Pérez in Tabasco State, Mexico. The recruitment was performed through a consecutive sampling approach, in a 2-year period from August 2016 to October 2018.

Ethical statement

All participants received verbal and written explanations of the study objectives; subsequently, they signed an informed consent. This study was approved by the ethics and research committee and the ethics committee of the High Specialization Regional Hospital Dr. Gustavo A. Rovirosa Pérez (00228/16).

The inclusion criteria were individuals over 18 years of age, both sexes; they had to be diagnosed with type 2 diabetes mellitus; they had to be under medical treatment for diabetes at the time of the study; they voluntarily agreed to participate in the study, and they all accepted and signed the informed consent. The exclusion criteria were individuals with type 1 diabetes mellitus and individuals diagnosed with depression who were under antidepressant treatment.

Clinical measures

First, all participants answered a semi-structured standard questionnaire to evaluate their sociodemographic characteristics (gender, age, civil status, socioeconomic status, occupation, years of education). Medical complications or comorbidities associated with diabetes mellitus (ischemic heart disease, renal disease, cerebrovascular disease, fatty liver, and diabetes neuropathy) were determined according to the clinical records of each patient. Also, patients were interviewed to identify the current use of alcohol and tobacco. Anthropometric measures including waist and hip circumference (in centimeters-cm) were obtained. Weight and height were measured to calculate the BMI according to the guidelines of the International Obesity Group [16]. We obtained fasting blood glucose (mg/dL) 2, total cholesterol (mg/dL), triglyceride levels (mg/dL), and glycated hemoglobin (HbA1c) as biochemical parameters for the present study. The biochemical parameters glucose, total cholesterol, and triglycerides were measured by spectrophotometry using a clinical chemistry analyzer (VITROS 4600, Ortho Clinical Diagnostics, Inc.). Besides, glycated hemoglobin was determined by an enzymatic immunoassay method (Human Glycated Hemoglobin A1c ELISA kit).

Evaluation of depressive symptoms

We measured depressive symptom severity using the Hamilton Depression Rating Scale (HAM-D) [17], which was applied by trained psychiatrists. The HAM-D allows an objective evaluation of depressive symptoms; it comprises 17 items assessed in a Likert scale. Each item has between three and five responses, with scores of 0–2 or 0–4, respectively. The HAM-D total score is the sum of each item's response and ranges from 0

(no depressive symptoms) to 52 (extreme depressive symptoms). This scale provides an overall score of the severity of depressive symptoms, which is classified according to the 2009 NICE Clinical Practice Guide [18] as follows: no depression 0–7 points, mild depression 8–13 points, moderate depression 14–18 points, severe depression 19–22 points, and very severe depression > 23 points. For the present study, we divided the sample using a cutoff point of 8, which identifies the presence of significant clinical depressive symptoms that need further clinical evaluation to identify a diagnosis of major depression which will require psychiatric treatment. The scale has adequate convergent validity for its use in Mexican individuals [19].

Statistical analysis

Demographic and clinical characteristics were expressed as frequencies and percentages for categorical variables while means and standard deviations were used for continuous variables. For the comparison between patients with and without clinical depressive symptoms, chi-square tests (χ^2) and independent sample *t* tests were used. Variables where significant differences arose between groups were entered in a multivariate logistic regression model using the backward conditional method to identify predictors of clinical depressive symptoms in individuals with type 2 diabetes mellitus. The Hosmer & Lemeshow test was used to determine goodness of fit of the regression model. We present the final regression model that included only those variables that remained significant after the backward stepwise process. Finally, a receiver operating characteristic curve (ROC) was plotted. The area under the ROC curve (AUC) was estimated and provided a summary measure to establish the diagnostic accuracy of HbA1c levels for depressive symptoms. All statistical values were deemed significant at $p \leq 0.05$. Analyses were performed using IBM SPSS Statistics 20.0 (IBM, Armonk, NY, USA).

Results

A total of 376 individuals were recruited. The majority of the participants were women (69.9%, $n = 263$), married (60.6%, $n = 228$), dedicated to household activities (48.7%, $n = 183$) with a mean age of 55.42 years (S.D. = 13.36, range 18–89 years), and a mean of 6.84 years of education (S.D. = 4.38, range 0–18 years).

Demographic, clinical, anthropometric, and biochemical variables between individuals with type 2 diabetes mellitus with and without symptoms of depression

The mean HAM-D score was 8.19 (S.D. = 7.44, range 0–31 points). Considering 8 points as the cutoff of the total score, 42.8% ($n = 161$) reported clinical depressive symptoms at the time of the study. From these, 40.9% ($n = 66$) showed mild depression; 32% ($n = 52$) showed moderate depression; 13.6% ($n = 22$) showed severe depression, and the remaining 13.3% ($n = 21$) reported very severe depression. The comparison of the main variables is presented in Table 1. In terms of demographic features, the participants with depressive symptoms were more frequently women, married, and younger. Substance use and anthropometric measures were similar in both groups. A higher number of participants with symptoms of depression exhibited medical complications including ischemic heart disease, renal disease, fatty liver, and diabetic neuropathy. Additionally, these participants had higher fasting blood glucose and higher HbA1c levels than those without clinical depressive symptoms.

Multivariate logistic regression analysis for the identification of predictors of symptoms of depression

We considered sex, age, and civil status for demographic variables; fasting glucose and HbA1C levels for biochemical parameters, and ischemic heart disease, renal disease, fatty liver, and diabetic neuropathy for comorbid conditions/medical complications for the regression model; these variables were included as explanatory variables for the presence of clinical depressive symptoms (Table 2 presents the final logistic regression model to predict symptoms of depression). The final regression model showed that being a woman, a younger age, being single, having ischemic heart disease, fatty liver, diabetic neuropathy, and higher HbA1c increased the risk of having clinical depressive symptoms in individuals with type 2 diabetes mellitus.

Diagnostic accuracy of HbA1C levels for symptoms of depression in individuals with type 2 diabetes mellitus

The use of HbA1c as a diagnostic test showed a low diagnostic accuracy, with an area under the ROC curve (AUC) of 0.59 (Fig. 1) and non-identifiable adequate cutoff points as expressed in low sensitivity and specificity values (Table 3).

Discussion

This study was conducted in a Mexican population to determine the prevalence of significant clinical depressive symptoms among individuals with type 2 diabetes mellitus. We found depressive symptoms in 42.8% of the

Table 1 Demographic, clinical, anthropometric and biochemical variables between individuals with type 2 diabetes, with and without symptoms of depression

Characteristics	All sample $n=376$	Without depression $n=215$	With depression $n=161$	Statistics
Demographic				
Age (years)	55.42 ± 13.36	56.68 ± 13.06	53.73 ± 13.60	**$t=2.11, p=0.03$**
Gender-women	263 (69.9%)	140 (65.1%)	123 (76.4%)	**$\chi^2=5.57, p=0.01$**
Marital status-married	226 (60.4%)	143 (66.5%)	83 (52.2%)	**$\chi^2=8.67, p=0.03$**
Occupation-household	183 (48.7%)	98 (45.6%)	85 (52.8%)	$\chi^2=3.39$, $p=0.49$
Years of education	6.84 ± 4.38	7.01 ± 4.30	6.60 ± 4.50	$t=0.89$, $p=0.37$
Substance use				
Smoking status-yes	23 (6.1%)	14 (6.5%)	9 (5.6%)	$\chi^2=0.14$, $p=0.70$
Alcohol status-yes	61 (16.2%)	32 (14.9%)	29 (18.0%)	$\chi^2=0.66$, $p=0.41$
Anthropometric measurements				
Weight (kg)	71.74 ± 16.72	72.06 ± 14.82	70.86 ± 17.12	$t=0.72$, $p=0.46$
Height (cm)	156.17 ± 9.58	156.58 ± 9.57	155.61 ± 9.60	$t=0.84$, $p=0.39$
Waist (cm)	98.29 ± 13.15	98.65 ± 12.34	97.80 ± 14.18	$t=0.61$, $p=0.53$
Hip (cm)	100.52 ± 10.95	101.26 ± 8.84	100.15 ± 10.62	$t=1.10$, $p=0.27$
Body mass index (BMI)	29.54 ± 7.39	29.38 ± 5.54	29.34 ± 7.21	$t=-0.07$, $p=0.94$
Biochemical				
Glucose (mg/dL)	181.63 ± 75.17	173.07 ± 70.34	193.06 ± 79.98	**$t=-2.52, p=0.01$**
HbA1c (%)	8.36 ± 2.23	8.08 ± 2.10	8.73 ± 2.35	**$t=-2.74$, p = 0.006**
Total cholesterol (mg/dL)	198.42 ± 56.39	199.51 ± 62.33	196.96 ± 47.47	$t=-0.45$, $p=0.65$
Triglycerides (mg/dL)	211.73 ± 137.59	216.15 ± 162.58	205.82 ± 94.62	$t=-0.77$, $p=0.44$
Medical conditions/complications				
Ischemic heart disease-yes	161 (42.8%)	82 (38.1%)	79 (49.1%)	**$\chi^2=4.49, p=0.03$**
Renal disease-yes	89 (23.7%)	42 (19.5%)	47 (29.2%)	**$\chi^2=4.75, p=0.02$**
Cerebrovascular disease-yes	23 (6.1%)	15 (7.0%)	8 (5.0%)	$\chi^2=0.66$, $p=0.41$
Diabetic neuropathy-yes	158 (42.0%)	73 (34.0%)	85 (52.8%)	**$\chi^2=13.41, p<0.001$**
Fatty liver-yes	49 (13.0)	18 (8.4)	31 (19.3)	**$\chi^2=9.62, p=0.002$**

Mean ± standard deviation or *n* (%)

Values in bold indicates significant statistical different

Table 2 Predictors of symptoms of depression in individuals with type 2 diabetes mellitus

Characteristics	β	S.E.β	OR	95% C.I		p
Gender-women	0.51	0.25	1.67	1.02	2.75	0.04
Marital status-single	0.61	0.23	1.85	1.18	2.91	0.007
Age	−0.02	0.009	0.97	0.95	0.99	0.006
HbA1c (%)	0.12	0.05	1.13	1.02	1.26	0.01
Ischemic heart disease-yes	0.56	0.23	1.75	1.10	2.77	0.01
Diabetic neuropathy-yes	0.82	0.22	2.27	1.45	3.55	<0.001
Fatty liver-yes	0.96	0.33	2.62	1.37	5.04	0.004
Constant	−1.87	0.84	0.15			

R^2 Nagelkerke = 0.178, Test Hosmer and Lemeshow $p=0.080$

study population. There are studies that have reported a high prevalence of depressive symptoms among individuals with type 2 diabetes mellitus just as it was observed in the present study [2, 20]. However, a study by Yasui et al., in Japan, reported a prevalence of depressive symptoms of 29.9%, which is much lower than the one we found [21]; nevertheless, it still indicates that individuals with diabetes have a higher risk of developing significant depressive symptoms than those without diabetes [13]. In consequence, it is necessary to pay more attention to

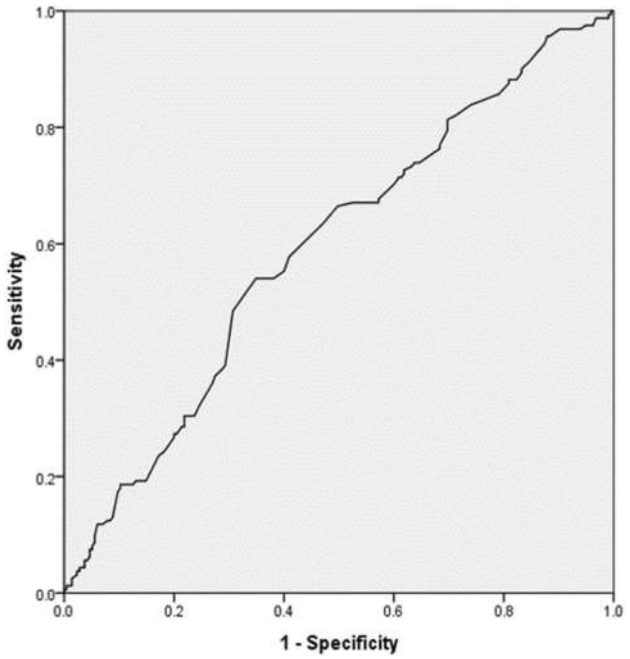

Fig. 1 The receiver operating (ROC) curve of HbA1C as a diagnostic test for symptoms of depression

the state of mind of individuals with type 2 diabetes mellitus and to continuously evaluate their mood.

Comparison of demographic, clinical, anthropometric, and biochemical variables

We also observed that women presented higher depressive symptom severity. Similar findings have been reported in several studies [20, 22]. Therefore, it is recommended to pay more attention to women with T2DM, since they have double risks of showing depressive symptoms than men [23, 24]. The higher prevalence of significant depressive symptoms in women can be attributed to different factors including social, cultural, biological, and hormonal [25]. For example, it has been observed that discrimination and gender roles may increase environmental stress especially in women. Thus, there is evidence that the imbalance between the ability to adapt to environmental demands and stress causes anatomical changes, release of immune mediators, and cardiovascular heart disease among other conditions [26].

The association between depressive symptoms and diabetic complications seems to be bidirectional. T2DM complications negatively affect the patient's health increasing the risk of having more severe depressive symptoms, which was observed in the present study [27]. Additionally, coexisting depressive symptoms in T2DM increase the risk of developing diabetic complications, such as retinopathy, nephropathy, neuropathy, sexual dysfunction, and macrovascular disease [28]. We found that complications in individuals with T2DM and depressive symptoms vary according to the region. Some studies have reported that micro- and macrovascular diseases are the main complications of individuals with diabetes [29, 30]. In addition, these diseases have adverse psychological effects among these individuals. Contrary to our results, there is a study that did not find any association between ischemic heart disease in individuals with T2DM, but they did find an association with neuropathy [31]. Another study reported that 86% of its study population (individuals with T2DM) did not present any complications; this, as a consequence of good glycemic control and of frequently attending medical evaluation [32]. In relation to the above, we consider it necessary to work more closely with individuals with T2DM and depressive symptoms, from prevention to diagnosis and timely treatment. Individuals with diabetes will benefit from a decrease of depressive symptoms and minor complications related to diabetes.

Also, we observed that glucose and HbA1c levels were associated with depressive symptoms. This was an expected result. A growing interest on this issue prompted a variety of studies showing that HbA1c levels are elevated

Table 3 Sensitivity and specificity of HbA1c cut-off points

Cutoff	Sensitivity	Specificity	False positive rate	False negative rate	Mistaken classification rate	Positive predictive value	Negative predictive value
6	0.94	0.13	0.87	0.06	0.52	0.45	0.75
6.5	0.85	0.21	0.79	0.15	0.34	0.49	0.62
7	0.76	0.32	0.68	0.24	0.49	0.46	0.64
7.5	0.70	0.40	0.60	0.30	0.47	0.47	0.64
8	0.63	0.53	0.47	0.37	0.43	0.50	0.66
8.5	0.52	0.67	0.33	0.48	0.40	0.54	0.65
9	0.36	0.73	0.27	0.64	0.43	0.50	0.60
9.5	0.27	0.80	0.20	0.73	0.43	0.50	0.59
10	0.24	0.83	0.17	0.76	0.43	0.51	0.59

in individuals with depression and T2DM, [12, 13, 33, 34] as was observed in the present report. However, until now, no conclusive outcomes have been attained. This suggests the need to continue evaluating HbA1C levels as a biomarker for depression in individuals with T2DM.

Predictive factors of depressive symptoms

We analyzed some predictive factors for clinical significant depressive symptoms in individuals with T2DM. Interestingly, we found that the levels of glucose and HbA1c were correlated with them. Our results are consistent to previous reports such as the one by Atif et al. [35], who indicated that these results are due to poor knowledge about the importance of maintaining optimal glucose levels. Several studies have observed that having and maintaining high levels of glucose and HbA1c, increase the severity of depressive symptoms, cause greater number of comorbidities, and are related to less adherence to treatment as well as to a lower quality of life [36, 37]. In relation to the above, we sought to define HbA1c levels as a diagnosis biomarker for clinical significant depressive symptoms.

Subsequently, we calculated the cutoff points for the clinical parameters mentioned above. Nevertheless, the results obtained from the ROC curve as well as the sensitivity and specificity values showed it is not an adequate diagnostic parameter for depressive symptoms in individuals with type 2 diabetes mellitus. However, its role as a predictor, in conjunction with other risk factors is a clinical relevance for the early identification, diagnosis, and treatment of depressive symptoms which should be further evaluated.

We recognized some weaknesses in our study. The number of participants could be considered small. Also, we did not have a control group. However, our case group consisted of well characterized and treated individuals in the diabetic clinic. This study was conducted in southeastern Mexico; therefore, generalizing to the entire Mexican population should be done with caution. Finally, a recent meta-analysis that analyzes depression in individuals with type 2 diabetes and obesity showed at least nine different measures to assess depression in the literature. We used HAM-D because it has been used and validated in the Mexican population [38].

Conclusions

We found a high prevalence of significant clinical depressive symptoms in Mexican individuals with type 2 diabetes mellitus, affecting more females than males. We also observed that the lack of glycemic control was associated to depressive symptoms in this Mexican population. Our data suggest an association between occurrence of depressive symptoms and ischemic heart disease, renal disease, diabetic neuropathy, and ischemic heart disease. On the other hand, gender, age, HbA1c levels, and medical complications were predictors for the presence of significant depressive symptoms in these Mexican individuals with type 2 diabetes. However, HbA1c levels showed low diagnostic accuracy for depressive symptoms in Mexican individuals with type 2 diabetes mellitus. Then, individuals that showed predictors of depression symptoms could be identified by the clinical medic and should request a psychiatric evaluation to identify if the individual requires specialized treatment for the presenting symptoms in order to avoid clinical complications associated with its presence and increasing individuals' well-being and quality of life.

Data Availability Data is available on request.

Declarations

Ethical Clearance This study was approved by the ethics and research committee and the ethics committee of the High Specialization Regional Hospital Dr. Gustavo A. Rovirosa Pérez (00228/16).

Conflict of interest The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Classification of diabetic retinopathy severity level using deep learning

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Abstract

Background Diabetic retinopathy (DR) is an eye disease developed due to long-term diabetes mellitus, which affects retinal damage. The treatment at the right time supports people in retaining vision, and the early detection of DR is the only solution to prevent blindness.

Objective The development of DR shows few symptoms in the early stage of progression; it is difficult to identify the disease to give treatment from the beginning. Manual diagnosis of DR on fundus images is time-consuming, costly, and liable to be misdiagnosed when compared to computer-aided diagnosis systems.

Methods In this work, we proposed a deep convolutional neural network for the recognition and classification of diabetic retinopathy lesions to identify the severity of the disease. The performance evaluation of the proposed model was tested with other machine learning classifiers such as K-nearest neighbor (KNN), Naïve Bayes (NB), logistic regression (LR), support vector machine (SVM), decision tree (DT), and random forest (RF).

Results Our proposed model achieves 98.5% accuracy for the recognition and classification of the severity level of DR stages such as no DR, mild DR, moderate DR, severe DR, and proliferative DR.

Conclusion The training and testing of our model are carried out on images from the Kaggle APTOS dataset, and this work can act as a base for the autonomous screening of DR.

Keywords Diabetic retinopathy · DCNN · Machine learning classifiers · Kaggle APTOS

Introduction

Diabetic retinopathy is a hostile impact of diabetes, which leads to vision-threatening problems if the treatment is not given at the right time. In healthcare, early detection of the disease is most important to provide better treatment. DR is a complexity of diabetes, which is the common cause of damage to the blood vessels that give nutrition to the retina. DR causes the blood vessels to become larger and seep fluids and blood from them. DR steers to permanent vision loss if left untreated in an early stage. Around the globe, due to DR, 2.6% of blindness occurs in people who have suffered from this illness for a long time.

To decrease the rate of blindness and spread awareness about DR, Rajiv Raman et al. [1] implemented a multi-center cross-sectional screening study for people aged over 40 and more in India. The authors did the screening in ten Indian states and one union territory for the duration of 16 months from December 2018 to March 2020. During their research, 42,146 people were screened. Out of those, 18.8% of the people were diagnosed with diabetes. Their study showed that the prevalence of DR is 12.5%, and for visually threatening DR is 4.0%. According to their research, in India, 3 million people with diabetes who are aged 40 years or older live with the risk of vision loss. World Health Organization (WHO) indicated that there are 77 million people in India over the age of 18 years who are suffering from type 2 diabetes, and

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25 million people are prediabetics, i.e., at high risk of growing diabetes population soon. More than 50% of people need to gain awareness about their disease status. Continuous retinal monitoring is most important for patients under treatment for diabetes in its early stage to prevent blindness. The disease's severity level can be identified by detecting small lesions formed in the retina of the DR-affected patients.

The presence of these lesions, such as hard exudates (HE), cotton wool spots (or) soft exudates (CWS), microaneurysms (MA), and hemorrhages (HM), indicates the severity level of the DR. MA is the prior indication of DR with tiny red circular dots in the retina as the vessel wall weakens. The size of the MA ranges from 125 µm with sharp margins. HM shows up with more prominent spots with a size exceeding 125 µm and irregular margins. HE presents as bright-yellow spots in the retinal outer layer, which are caused by leakage of plasma and have sharp margins. CWS seems to be white spots originating from nerve fiber swelling with round or oval shapes. Based on their appearance in color, these lesions are categorized as red (MA and HM) and bright lesions (HE and CWS). Based on the presence of these lesions, the severity level of the disease can be identified as no DR, mild DR, moderate DR, severe DR, and proliferative DR. The severity level of DR and the formation of lesions in the retina are presented in Fig. 1, Table 1, and Fig. 2, respectively.

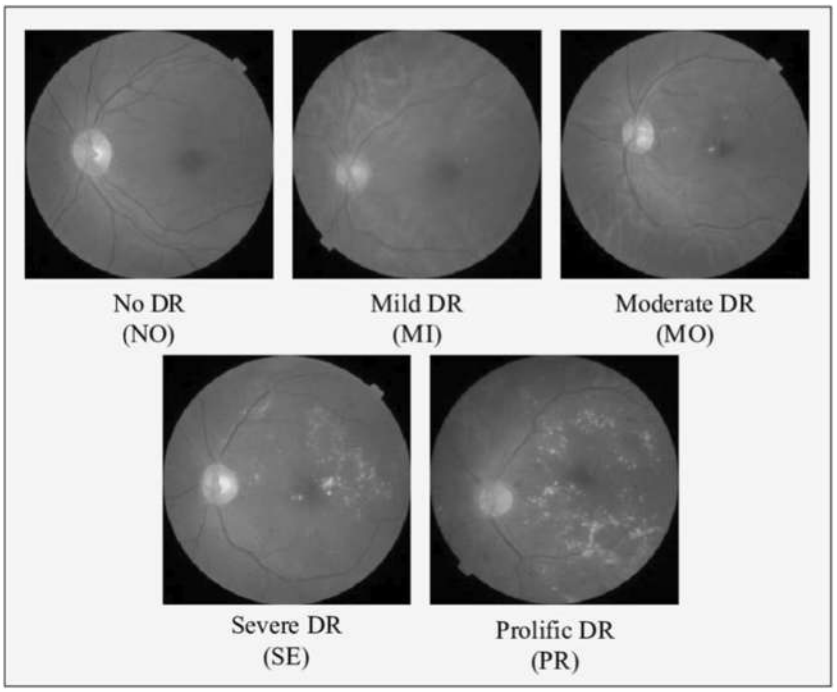

Fig. 1 Severity level of DR. Sample image from APTOS dataset

Table 1 Severity level of DR based on the presence of lesions

Severity stages	DR severity level	Lesions presence
Stage 0	No DR	Absence of lesions
Stage 1	Mild non-proliferative DR	MA alone
Stage 2	Moderate non-proliferative DR	More than just MA but less than severe DR
Stage 3	Severe non-proliferative DR	Anyone: • more than 20 intraretinal HM in each of the four quadrants • definite venous beading in 2 + quadrants • Prominent intra-retinal micro-vascular abnormalities in 1 + quadrant • no signs of proliferative DR
Stage 4	Proliferative DR	One or more: • Vitreous/pre-retinal HM, neovascularization

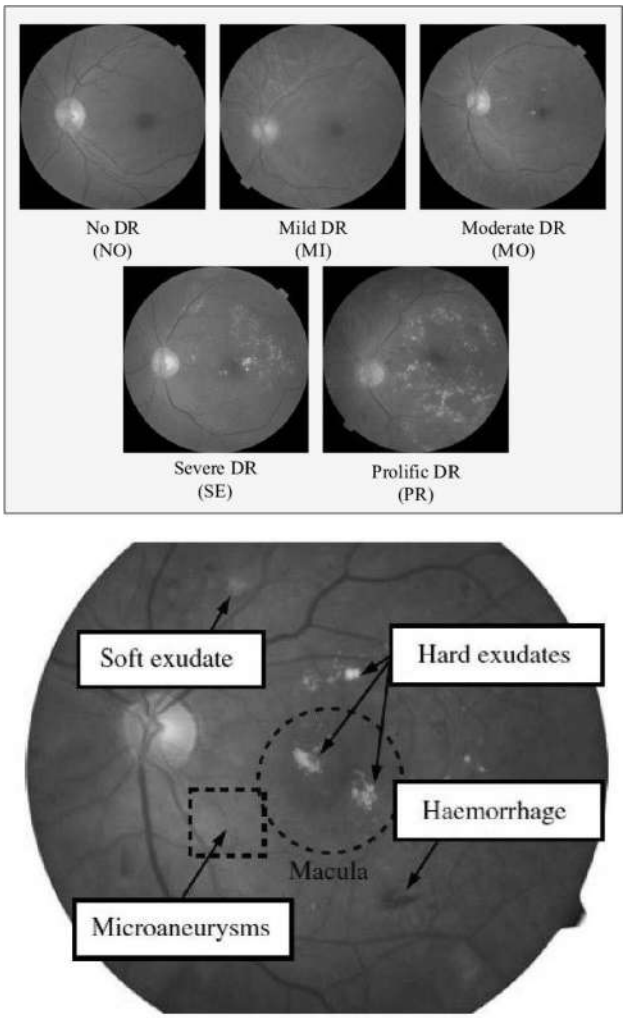

Fig. 2 Lesions formed in the retina due to DR

In the severity level, stage 1 is the earlier one, where the formation of MA can occur. In the next stage, with the advancement of the disease, the vision got blurred due to swelling in the blood vessels. In the next stage, aberrant blood vessel growth can be identified. In the severe DR stage, many blood vessels are blocked. The proliferative DR is an advanced stage where retinal detachment occurs with a retina break, leading to complete vision loss. Regular retinal screening is necessary to treat this disease in the earliest stage to retain vision.

Currently, manual diagnosis is performed with a comprehensive dilated eye exam. In this screening test, eye drops are applied to the eye to widen the pupils and get a better view of the inner part of the eyes. After that, a dye is injected into the body to check blood vessels in the eyes. By this, manual grading can be done to identify the presence or absence of DR. This manual diagnosis is time-consuming, costly, and requires human expertise. The diagnosis of DR is easy and affordable when it is automated. In this work, the diagnosis of DR severity can be identified with deep learning techniques to make the process more efficient by saving cost and time.

The flow of this paper is organized as follows. "Related works" briefly discusses the related works, while "Methodology" presents the methodology to classify the severity level of DR using deep learning techniques. "Experimental results" describes the performance measure of the proposed work, while "Performance evaluation analyses" shows the results and discussion. The conclusion summary is presented in "Conclusion and future work."

Related works

Using machine learning models is very helpful in solving many issues related to image classification [2] in healthcare work and particularly in disease predictions [3]. A greater number of works have been proposed to detect DR using machine learning techniques [4] such as SVM [5] and decision tree [6].

Previously, various methods have been used to classify normal and abnormal retinal images with DR. Deep learning is an essential and efficient platform for performing automated and reliable decision-making tasks [7]. Deep learning models such as convolutional neural networks have been proposed for deep feature extraction and image classification applications [8–10]. Qiao et al. [11] presented their research to detect MA for the DR grading system, including mild non-proliferative diabetic retinopathy (NPDR), moderate NPDR, and severe NPDR using DCNN. Saranya and Uma Maheswari [12] proposed their work with convolution neural network (CNN) to classify images into four phases of DR.

Zhang et al. [13] and Hemanth et al. [14] proposed their work on classifying DR stages in the retinal images into four classes. However, the severity levels used in both works are different. Zhang et al. used four severity levels of DR N:o DR, mild NPDR, moderate NPDR, severe NPDR, and PDR. At the same time, Hemanth et al. presented their classification of the retinal images into normal, macular edema, PDR, and NPDR.

Based on the literature study, it is visible that developing an automated diagnosis system for detecting DR is a must to identify the disease severity at an early stage. Considering the importance, the objective of this research work is proposed. We aim to develop a robust and efficient model for the recognition and classification of DR severity stages using the Kaggle APTOS 2019 dataset [15]. The proposed work could minimize the time for effectively diagnosing the disease with less cost.

Methods and Materials

The early detection of DR severity stages plays a vital role in better treatment. As an initial step, the dataset selection can be done. For our research work, the APTOS 2019 Kaggle dataset was used to recognize and classify the severity level of DR. The dataset images were taken using fundus photography under varying illumination conditions. These images are manually graded as class 0 to class 4 to indicate various severity levels. The number of images available in the dataset for each severity level is listed in Table 2.

From the total of 3,662 images, 75% of the images were used for training purposes, and the remaining 25% of the retinal images were used for testing purposes. Furthermore, the image preprocessing procedure includes adding more images using augmentation techniques [16] to reduce overfitting errors and noise during the training phase. This work used the following image augmentation techniques to classify DR stages. The augmentation takes place with image rotation, color transformation, width shifting and height shifting, zooming, horizontal flipping, and blurring operations to generalize the model well for recognition of DR severity stages. The database is then expanded with the augmented images and the images from the expanded database for the training and testing phase.

In this proposed work, the detection of the severity level of diabetes with DCNN is performed on the APTOS 2019 database images plus augmented images, and the results are compared with popular image classification techniques, including SVM, KNN, DT, RF, LR, and NB. The flowchart of the proposed DL-based DR stages classification is shown in Fig. 3.

DR severity stage classification using DCNN

The recognition of DR severity level can be achieved through CNN to extract features from a retinal color fundus image collected from the APTOS Kaggle database for identifying DR stages from class 0 to class 4. The deep convolutional neural network consists of convolutional layers, a pooling layer, fully connected layers, and dense layers of output neurons with a softmax layer. This work applies the input RGB image to the first convolutional layer with a neuron size of $224 \times 224 \times 3$.

Table 2 Summary of retinal images with a severity level of DR from the APTOS dataset

Severity level of DR	Number of image samples
Class 0 (normal)	1805
Class 1 (mild stage)	370
Class 2 (moderate stage)	999
Class 3 (severe stage)	193
Class 4 (proliferative stage)	295
Total	3662

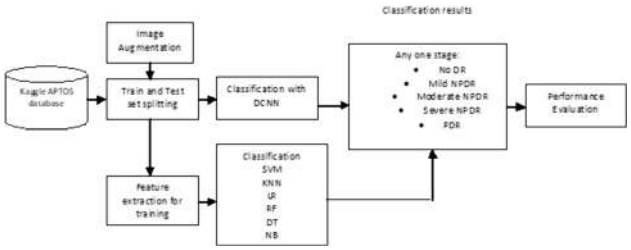

Fig. 3 Flowchart for the proposed DR stage classification work

The proposed DCNN architecture is given in Fig. 4. Then, the input image is allowed through a stack of the convolutional layer with a "relu" activation function where the filter uses the small receptive field as 3×3 with the convolution stride of one pixel. The padding is chosen to preserve the spatial resolution throughout the convolutional layers to extract 32 feature maps with the pool size of 2×2. "Relu" stands for rectified linear unit, which is used for learning non-linear real-world data. The second and third convolutional — relu with maximum pooling layers use the same 3×3 kernel, resulting in 64 and 128 feature maps with the convolution stride of one pixel and the padding chosen as the same to produce the output of the same size as the input. The fully connected layer uses the SoftMax activation function for classifying the retinal images into five classes. In DCNN, the stochastic gradient descent (SGD) algorithm is used with a cross-entropy cost function for properly tuning hyper-parameters. The dropout value is set as 0.5 in the convolutional layers and 0.25 in the fully connected layers to avoid overfitting issues during training.

Implementation

In this work, the identification of severity stages has been completed through the training of the DCNN by assigning

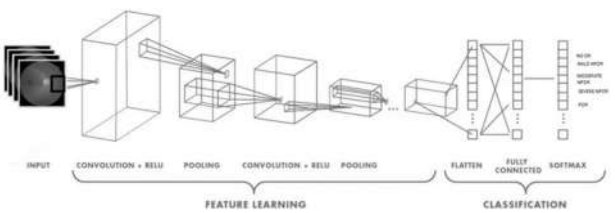

Fig. 4 The proposed DCNN architecture

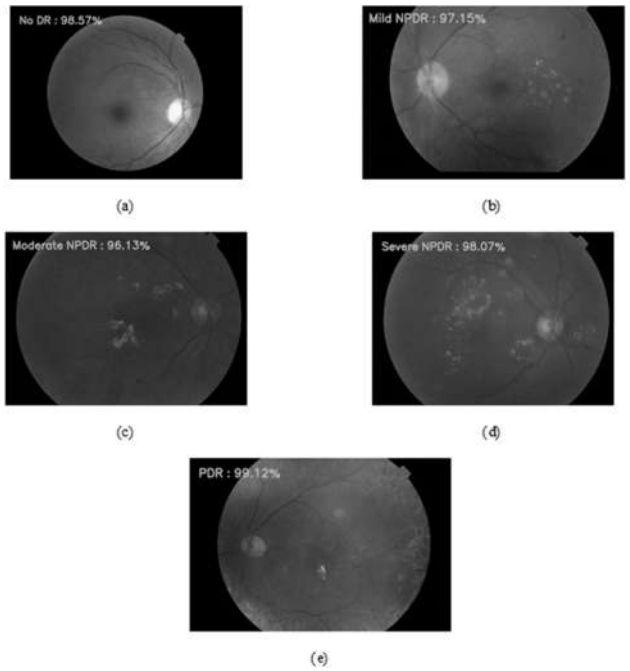

Fig. 5 Recognition results for severity stages of DR from retinal images: **a** no DR; **b** mild DR; **c** moderate DR; **d** severe DR; **e** PDR

a proper feature matrix and obtaining the target class based on the input class of the dataset. The images collected from the dataset with respective labels have been given as input to DCNN with a learning rate of 0.001 and trained for 50 epochs with a batch size of 32.

Results and Discussion

In this section, the performance of the proposed method was evaluated and analyzed. However, the recognition rate in this proposed method is excellent, with the images used from the expanded image database for training and testing. The proposed algorithm classifies the severity stages of DR using the DCNN algorithm with an accuracy of 99%. Some of the images from the other datasets, such as DRIVE and images from the Google search engine, have been tested with the proposed model to evaluate the performance of our work. The classification of DR severity stages from class 0 to class 4 was successfully done in the proposed work. From these experimental results, it is visible that this algorithm can classify the severity stages of DR in real-time and is helpful for the early detection of DR with less cost and time.

Table 3 Performance comparison of the various classifiers with different performance metrics

Name of the classifier	Classes	Precision	Recall	F1 score
DCNN	No DR	99	97	98
	Mild NPDR	100	99	99
	Moderate NPDR	98	100	98
	Severe NPDR	100	100	100
	PDR	99	99	99
SVM	No DR	90	93	91
	Mild NPDR	92	94	93
	Moderate NPDR	94	94	94
	Severe NPDR	100	97	99
	PDR	94	95	94
KNN	No DR	98	97	98
	Mild NPDR	100	100	100
	Moderate NPDR	100	94	97
	Severe NPDR	95	100	97
	PDR	96	98	97
DT	No DR	90	97	94
	Mild NPDR	90	100	95
	Moderate NPDR	86	91	88
	Severe NPDR	100	89	94
	PDR	81	70	75
NB	No DR	85	82	80
	Mild NPDR	71	86	77
	Moderate NPDR	84	68	75
	Severe NPDR	78	80	79
	PDR	88	75	81
RF	No DR	87	83	85
	Mild NPDR	76	80	78
	Moderate NPDR	78	71	74
	Severe NPDR	84	76	80
	PDR	80	74	77
LR	No DR	95	97	96
	Mild NPDR	96	94	95
	Moderate NPDR	95	96	95
	Severe NPDR	98	93	95
	PDR	97	96	96

DR recognition and severity level prediction

The experimental part of this proposed work is divided into two main tasks. Task 1 involves the presence or absence of DR, which was identified. Another task is to predict the severity level of the DR stages using retinal images. For Task 1, the system must identify whether

Table 4 Performance comparison of various classifiers concerning Accuracy

Model	Accuracy (%)
DCNN	98.5
K-NN	97.6
SVM	96.4
LR	95.5
DT	87.5
RF	84
NB	82.7

the patient has suffered with DR. In this work, the DR images from the dataset were labeled as the name of the disease's severity level. The remaining normal images are labeled as no DR and recognized successfully by our algorithm with a good detection score. Furthermore, identifying the severity level is most important to give better treatment. Hence, the classification of the severity level of DR for five different classes is carried out in the next task.

The severity level classification of DR was done on an expanded image dataset developed for this work with augmented images and the images from the APTOS Kaggle dataset with variations in illumination and brightness. The proposed work to detect the severity level of DR is performed on the laptop with the configurations of Intel Core i7-CPU@ 4.5 GHz and Google Colab. The programs for training and testing DR images were written in Python with OpenCV on the Microsoft Windows 10 operating system. The experimental tests were carried out on images listed under three categories in the Kaggle dataset such as test_images, train_images, and val_images. Some of the results were also presented in Fig. 5 for the recognition of DR severity stages.

The severity stages of DR were tested with the proposed algorithm, and it was observed that the results were better when compared with other classification methods such as SVM, KNN, DT, LR, RF, and NB. Comparing the experimental results, the performance of NB was low among all the other methods. The proposed method can accurately detect the stages from class 0 to class 4. The NB method is unable to detect more abnormalities in the images. The experimental results indicated that the DCNN method is suitable for recognizing all DR stages with high detection accuracy.

The normal retinal images with no abnormalities were utilized during testing to meet the real-time challenges. To check the same, 20 images that did not contain DR were collected and tested to test the performance of the proposed algorithm from the Google search engine. The recognition method with DCNN found no abnormalities in these images, with a detection score of 98.57%.

From the experimental results, it is clear that our proposed DCNN model adequately detected the severity stages of DR with a detection score of 97.15% for mild NPDR, moderate NPDR at 96.13%, and severe NPDR at 98.07%, PDR at 99.12%. The results of this experiment further revealed that the DCNN model was the most suitable for detecting all stages of DR, mainly when there were minor abnormalities along with complex backgrounds in the retinal images. The RF method struggled to recognize the lesions well, but it performed better when compared with the NB method. These two methods needed help to recognize the severity stages positioned at various locations in the images and lesions that were grouped and close together with other objects.

Nevertheless, some lesions are misidentified in the retinal images for some severity levels, and the images vary in illumination in real-time. These issues will be resolved in the future by adding more retinal images in the database to improve learning with this vision-based technique, meet real-world challenges, and make this model more suitable for detecting more vision-threatening issues. The performance evaluation analyses were conducted, and the results were discussed in the forthcoming section.

Performance evaluation analyses

Classification of DR

The object recognition algorithm's performance depends on the classifier's performance. The analysis was evaluated by calculating the statistical indicators, including accuracy, precision, recall or sensitivity, and F1 score.

$$\text{Accuracy} = \frac{\textit{True Positives} + \text{True Negatives}}{\textit{True Positives} + \text{True Negatives} + \textit{False Positives} + \text{False Negatives}}$$

$$Precision = \frac{True\ Positives}{True\ Positives + False\ Positives}$$

$$Recall = \frac{True\ Positives}{True\ Positives + False\ Negatives}$$

$$F1\ Score = 2.\frac{Precision \times Recall}{Precision + Recall}$$

The performance comparison of the DCNN with other classifiers with performance metrics such as precision, recall, and F1 score measures is presented in Table 3. According to the classification metrics obtained from the validation step, the F1 score value of the DCNN for the classification of no DR, mild NPDR, moderate NPDR, severe NPDR, and PDR was 98, 99, 98, 100, and 99, and the overall F1 score achieved by the algorithm was 99% respectively. The results of the

proposed work showed that the DCNN classification algorithm is better than other classifiers such as SVM, KNN, DT, LR, RF, and NB for the classification of DR severity levels taken from the expanded retinal fundus image dataset.

Furthermore, the performance comparison related to accuracy is presented in Table 4. The experimental results witnessed that DCNN can recognize the major severity stages of DR. This underlying work acts as a base to detect the lesions present in the retinal fundus image in real time for the grading of DR in an automated manner.

The proposed DCNN algorithm performed well in the accuracy part, and it offers a good accuracy of 98.5% with no over-fitting issue by applying data augmentation and dropout techniques during training.

Conclusion

This paper proposed a DR severity stage recognition and classification algorithm using the DL technique with the APTOS Kaggle dataset. In the proposed method, the severity stages were efficiently predicted from retinal fundus images. We evaluated the performance challenges by checking the algorithm with other dataset images, such as the DRIVE dataset and retinal fundus images from the Google search engine, and concluded that the proposed model can classify the severity level of DR successfully. Hence, the proposed method efficiently predicts DR with an accuracy of 98.5%. The detection of the lesions in the retinal fundus images using deep learning-based object detectors will be considered as future work to perform the grading of DR automatically without manual guidance.

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Declarations

Conflict of interest The authors declare no competing interests.

Ethical clearance In this research work, we have utilized images from the Kaggle APTOS dataset and carried out the experimental work. And hence, the consent of patient, Ethical clearance are not required. In future, we will evaluate the performance of our work on real-time images.

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SHORT ARTICLE

Correlation of presence and severity of glucose derangements with severity of Liver Cirrhosis: a hospital-based cross sectional observational study from New Delhi

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Abstract

Background Association between liver cirrhosis (LC) and glucose intolerance has been known since long. Many studies in the past have attempted to explore the correlation of glucose metabolism disorders (GMD) with the severity of LC with mixed results (some favouring i.e. higher prevalence of GMD in more severe LC; others negating). This study was conducted to shed further light on the significance of this association.

Objective This study has been carried out with the aim of studying the correlation between GMD and the severity of LC, as determined by the Child-Turcotte-Pughe (CTP) score.

Methods 100 patients with LC admitted in medical wards were studied and tested with fasting plasma glucose (FPG), 2 h post-75 g oral glucose load plasma glucose (PPG), glycosylated haemoglobin (HbA1c) and fasting plasma insulin. They were categorized based on the severity of LC into CTP A, B or C class and then patients belonging to different classes were compared for the presence of GMD and insulin resistance (IR).

Conclusion Out of 100 patients, 6, 21 and 73 were respectively found as falling under CTP class A, B and C of LC. The frequency of diabetes mellitus (DM) was found to progressively increase with worsening grade of cirrhosis (17%-A, 24%-B and 27%-C), however this was not significant (p value 0.82). The p values for IR, GMD (pre-diabetes or DM), pre-diabetes (pre-DM) were 0.629, 0.382 and 0.189 respectively. To conclude, development of GMD and IR may be independent of the severity of LC. However more studies may be required to further study this association.

Keywords Liver cirrhosis · Glucose metabolism disorders · Severity · Diabetes mellitus · Insulin resistance

Introduction

Association between liver cirrhosis (LC) and glucose intolerance has been known since long. This association includes not only patients of LC developing glucose metabolism disorders (GMD) but also known diabetics developing liver disease progressing to cirrhosis. GMD refer to a spectrum of abnormalities in glucose tolerance. These include asymptomatic pre-diabetes mellitus (Pre-DM) which can be present either in the form of impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) as well as overt diabetes mellitus (DM).

Cirrhosis is characterized by an increased burden of inflammation. On the other hand, conditions that are characterized by GMD or insulin resistance (IR), such as DM, metabolic syndrome, non-alcoholic fatty liver disease (NAFLD) and pregnancy are also associated with high inflammatory burden. Thus, a link between cirrhosis and impaired glucose metabolism could exist via the inflammatory pathway.

Evidence implicating systemic inflammation in the pathogenesis of cirrhosis is compelling. Easily measured serum markers (procalcitonin, CRP: lymphocyte count ratio, SIRS) and certain clinical parameters (total leucocyte count, mean platelet volume, neutrophil: lymphocyte ratio) have been studied as prognostic tools in cirrhosis for follow-up, monitoring and management.

Hyperglycaemia in DM per se leading to progression of liver disease to fibrosis in NAFLD was found to be related to overexpression of connective tissue growth factor (CTGF), which then likely induces the transcription of several ECM

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Table 1 The WHO Criteria For Diagnosing DM/ IFG/ IGT

Condition	Fasting plasma glucose	2 h-post 75 g oral glucose load plasma glucose	HbA1c	
Unit	mmol/L (mg/dL)	mmol/L (mg/dL)	mmol/mol	%
Normal	< 6.1 (< 110)	< 7.8 (< 140)	< 42	< 6.0
IFG	≥ 6.1 (≥ 110) & < 7.0 (< 126)	< 7.8 (< 140)	42–46	6.0–6.4
IGT	< 7.0 (< 126)	≥ 7.8 (≥ 140) but < 11.1 (< 200)	42–46	6.0–6.4
DM	≥ 7.0 (≥ 126)	≥ 11.1 (≥ 200) and/or,	≥ 48	≥ 6.5

(extracellular matrix components) components. Also insulin brings about induction of CTGF in hepatic stellate cells (HSC); IR and reactive hyperinsulinaemia being present in all cirrhosis patients irrespective of aetiology. Many pro-inflammatory cytokines are up regulated whereas the anti-inflammatory ones are decreased.

World over, in many studies analysing this association, the prevalence of GMD as well as IR was found to be associated closely with the Child-Turcotte-Pughe score (CTP score), with increasing prevalence with worsening grade of LC. Certain others found no association between the two. Hence, this study was planned to examine this further.

Materials and methods

A hospital-based cross-sectional observational study was conducted in the department of General Medicine, Lady Hardinge Medical College & Sucheta Kriplani Hospital, New Delhi from November 2015 to April 2017 wherein 100 adult in-patients with LC were enrolled after taking a written informed consent.

Sample size was calculated using the formula :

$$n = (1.96)^2 pq/E^2 \text{ at } 95\% \text{ confidence level}$$

Considering the fact that the prevalence of GMD in hospitalized cases of LC was reported by various studies between 33–96% [1–4] and also presuming the estimated prevalence as 70%, at 95% level of significance with an allowable error of 15% (of 70%) the calculation of statistically valid sample size was done as follows: p was the probability of GMD in patients of LC (0.7), q was the complement of p i.e. 1-p (0.3) which reflected liver cirrhosis free of GMD.

$$n = 1.96^{*}1.96^{*}0.7^{*}0.3/\left(15/100^{*}0.7\right)^2$$
$$= 73.17 \text{ or } 74$$

Applying a 10% drop out/ non response to this (which included loss to follow-up due to leave against medical advice/ absconding), sample size should have been 81.4 or 82. A final sample size of 100 was taken in view of availability of cases and better credibility.

LC was diagnosed by a combination of clinical/ biochemical/ radiological findings: patients with clinical signs of liver cell failure or clinical features of portal hypertension with hypoalbuminemia, reversal of albumin and globulin ratio (A:G ratio), deranged prothrombin time (PT) and international normalized ratio (INR); ultrasound abdomen showing surface nodularity, coarse/altered echo texture, parenchymal inhomogeneity in the liver without or with ascites alone or with features of portal hypertension like portal vein diameter ≥ 13 mm, presence of collaterals and splenomegaly. Patients who were suffering from hepatocellular carcinoma, acute/ chronic pancreatitis/ pancreatic cancer or endocrinopathies (such as Cushing's syndrome, acromegaly, glucaganoma, pheochromocytoma, polycystic ovarian syndrome) or who had undergone pancreatectomy were excluded. Also excluded were those on corticosteroids or those who had received it within the last 48 h.

- History, clinical examination and investigations were recorded as per a pre-defined proforma. All the study patients were subjected to fasting plasma glucose (FPG) and fasting plasma insulin and 2 hours-post 75 grams oral glucose load plasma glucose (PPG). Glucose metabolism disorders were diagnosed if the patient was a known DM/ Pre-DM (IGT/ IFG) or was detected to have DM/ Pre-DM after entering the study. The criteria (WHO [5]) that were used for diagnosing DM, IGT and IFG are as follows: (Table 1)

Those with symptoms suggestive of DM and one abnormal fasting or post prandial value were labelled as having GMD. In case of an asymptomatic patient, one abnormal value was followed by a repeat next day testing. Patients were labelled as GMD only if both reports were abnormal. IR was calculated using the homeostatic model assessment-insulin resistance formula (HOMA-IR) which is given below:

Table 2 Criteria For CTP Scoring

SCORE	1	2	3
Serum bilirubin (mg/dl)	< 2.0	2.0–3.0	> 3.0
Serum albumin (g/dl)	> 3.5	3.0–3.5	< 3.0
Prothrombin time (seconds prolonged)	0–4	4–6	> 6
Ascites	None	Easily controlled	Poorly controlled
Hepatic encephalopathy	None	Minimal	Advanced

- For patients found to be having GMD, appropriate treatment required for controlling plasma glucose was provided and noted.

Biochemical methods used for various estimations: Blood glucose by glucose oxidase peroxidase method, glycosylated haemoglobin by latex agglutination method (NGSP certified)using the D-10 instrument, fasting plasma insulin by electro chemiluminescence immunoassay, PT-INR-apTT by ACL elite pro machine, serum bilirubin by modified Jendrassik's method, albumin by dye- (bromcresol green) binding method.

$$\text{HOMA} - \text{IR} = \text{FPG (mg/dL)}^{*}\text{Fasting Plasma Insulin (microU/mL)}/405$$

A HOMA-IR cut off of 2.5 was taken (Singh Y et al. [6]) for diagnosing insulin resistance.

- The severity of liver disease was assessed using the CTP score. [7] (Table 2)

The CTP score was calculated by adding the scores of the five factors (range from 5 to 15). Child Pugh class can be A, B or C. Decompensation indicates cirrhosis with a Child–Pugh score ≥ 7 (class B). This level has been the accepted criterion for listing for liver transplantation.

Class A CTP: scores 5 and 6
Class B CTP: scores 7 to 9
Class C CTP: scores 10 or more

Patients belonging to different classes were compared for the presence of GMD.

- All in-patients of LC had their blood sugar testing at least twice once at admission and again prior to discharge to check for the presence of stress induced hyperglycaemia.

Statistical analysis

Categorical variables were presented in number and percentage (%). Qualitative variables were correlated using Chi-Square test/ Fisher's exact test. A p value of < 0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was performed using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

Out of 100 patients, 6, 21 and 73 were respectively categorized as CTP grade A, B and C of LC. The frequency of DM was found to progressively increase with worsening grade of cirrhosis (17%, 24% and 27%, respectively for CTP Grade A, B and C), but the increase was not significant (p value = 0.82). Likewise, association of severity of liver cirrhosis was not significant with GMD or Pre DM (Table 3).

Likewise, no significant association between increasing severity of LC and IR was found; *p* value = 0.629 (Table 4).

Out of the 100 patients studied, 26 were found to have DM (15 were newly diagnosed, while 11 were previously diagnosed cases).

Table 3 GMD And Severity Of Liver Cirrhosis

Severity of LC	Total	GMD			
		No	Yes	Pre DM	DM
A	6	5 (83.33%)	1 (16.67%)	0 (0.00%)	1 (16.67%)
B	21	11 (52.38%)	10 (47.62%)	5 (23.81%)	5 (23.81%)
C	73	45 (61.64%)	28 (38.36%)	8 (10.96%)	20 (27.40%)
Total	100	61 (61.00%)	39 (39.00%)	13 (13.00%)	26 (26.00%)
p value	-		0.382	0.189	0.82

$\chi 2 = 1.926$, df = 2

Table 4 IR And Severity Of LC

Severity of LC	Total	IR	
		No	Yes
A	6	5 (83.33%)	1 (16.67%)
B	21	14 (66.67%)	7 (33.33%)
C	73	55 (75.34%)	18 (24.66%)
Total	100	74 (74.00%)	26 (26.00%)

$\chi 2 = 0.927$, df = 2, p value = 0.629

Discussion

In the present study, increasing trend in DM was observed with increasing severity of cirrhosis (approximately 17%, 24% and 27% in CTP Grade A, B and C, respectively), but it did not reach statistical significance. Hence, no significant increase in the frequency of GMD (both pre-diabetes and DM) could be demonstrated with worsening grade of liver disease. However, in the review of available literature, a majority of studies [8–14] were found favouring a positive correlation between the severity of liver disease and the occurrence of GMD, i.e. more severe the liver disease, a greater proportion of subjects were found to have GMD. Caronia S et al. [8] demonstrated the percentages of the population with cirrhosis due to HCV found to have DM as approximately 10%, 22% and 32%, respectively for Child Pugh A, B, C; similarly, for cirrhosis due to HBV the statistics were 4.5, 8.9 and 12.8%, respectively. In a study of 121 cirrhotic patients from central India (Vasepalli P et al. [15]), the presence of hepatogenous diabetes was found to be well associated with the severity of cirrhosis in the form of higher MELD score (> 15) and CTP score (> 10). In yet another 2017 study [16] of 100 patients with CLD from Kolkata, significant association between impaired glucose tolerance and diabetes mellitus with the severity of CLD (based on CTP score) was found (p value < 0.05).

Only a few studies (Mukherjee S et al. [17], Muller MJ et al. [18]) had findings similar to the present study. Also in a study done at Mayo Clinic Rochester between Jan 2006 and Dec 2011 (Yang JD et al. [19]), one of the findings was that the severity of hepatic decompensation determined by the mean CTP and the MELD scores was lower in patients with diabetes mellitus as compared to those without it.

In the present study, no significant association between increasing severity of LC and IR was found in the present study. Few studies support this finding, [18, 20] whereas others [21–23] suggest that prevalence of IR increases with increasing severity of liver disease. In a study [24] published in 2020, IR was observed in 20 (74%) cirrhotic patients and CTP C patients had higher HOMA-IR than those with Child class B cirrhosis; however, this difference was statistically insignificant (p = 0.07). In yet another study done in Amritsar [25] on 100 non-diabetic patients with cirrhosis, a significant increase in IR was noted in patients with increased CTP score and advanced disease.

Many studies from reviewed literature were found to have explored and found inflammation to be a significant factor associated with chronic liver disease including cirrhosis. For instance, in a retrospective study [26] done comparing patients of chronic hepatitis C with healthy controls and also patients of chronic hepatitis C with or without significant fibrosis, a significant positive correlation was found between CRP to lymphocyte count ratio (an inflammatory marker) and APRI score (a non-invasive index of fibrosis).

Likewise, other conditions characterized by IR and GMD also have high inflammatory burden. Human studies of neuregulin-4 (which is believed to have anti-atherogenic and anti-inflammatory properties) have suggested its association with insulin resistance, impaired glucose metabolism, obesity, NAFLD, DM and metabolic syndrome. In a study [27] to observe the relationship of neuregulin-4 and control of diabetes, neuregulin-4 was found to be significantly increased (as a part of physiologic protective overexpression) in patients with poorly controlled DM vis-ă-vis well controlled DM and controls. Association between low-grade inflammation related to obesity and metabolic syndrome with its attendant complications has been well studied. In another study [28] conducted to assess mean platelet volume as an inflammatory marker in well and poorly controlled DM, it was found to positively and strongly correlate with both HbA1c & FPG. Uric acid is known to be an inducer of insulin resistance and a sensitive marker of underlying inflammation. A proposed novel marker-uric acid to HDL cholesterol ratio (UHR) was found to be significantly lower in well controlled DM as compared to poorly controlled DM in a study. [29] Furthermore, sensitivity and specificity of UHR in predicting metabolic syndrome were found to be better than most of the sensitivities and specificities of the five criteria of metabolic syndrome. UHR was also significantly higher in NAFLD compared to healthy controls; it was suggested that elevated UHR levels should be considered a useful tool in diagnosing hepatic steatosis [30].

Conclusion

Though a rising trend was demonstrated in the frequency of GMD with higher grade of cirrhosis, this association did not reach a significant level. More studies with a larger sample size might help in checking this further. However for now, we conclude that the development of GMD and IR may be independent of the severity of LC. Nevertheless, we suggest that presence of GMD and IR should be screened in all cirrhosis patients irrespective of the severity class.

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Declarations

Ethical approval This study was approved by institutional ethical committee.

Conflict of interest The authors have no relevant financial or non-financial interests that are directly or indirectly related to this work to disclose.

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CASE REPORT

Severe limited joint mobility (LJM) involving both the hands and feet in type 1 diabetes mellitus

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Abstract

Objective Limited joint mobility (LJM) is one of the most common disabling musculo-skeletal complications in long-standing diabetes. Though it has been described extensively in previous pieces of literature, symmetrical involvement of both upper and lower limbs hasn't been much reported in recent accounts.

Case presentation A 25-year-old boy with type 1 diabetes mellitus (T1DM) (diagnosed at 14 months of age with poor glycemic status) had presented with progressive flexion deformity of both upper and lower limbs. It had started from the little fingers of both hands followed by the involvement of the other finger and toes. It was associated with tight and waxy skin. There was no history of trauma, pain, redness or morning stiffness. On examination, symmetrical contractures of metacarpo-phalangeal and inter-phalangeal joints of all the fingers along with the involvement of metatarso-phalangeal and inter-phalangeal joints of foot were found. These LJM findings were classified as stage III as per Brink-Starkman classification. Further examination revealed bilateral moderate nonproliferative retinopathy and proteinuria. The patient was started on palmar-stretching exercises along with reinforcement of adequate glycemic control and relative improvement was noted after 6 months.

Conclusion LJM has been found to be consistently associated with microvascular complications of diabetes. Its chief pathogenesis is abnormal cross-linking of collagen fibers. The uniqueness behind this description lies in the advanced presentation of LJM involving both the hands and feet. This case also illustrates the need for regular checks for musculoskeletal involvement in T1DM, which are frequently missed.

Keywords Limited joint mobility · Type 1 diabetes mellitus · Upper and lower limbs

Introduction

Limited joint mobility (LJM) is a common musculoskeletal manifestation of diabetes. It is frequently associated with microvascular complications like neuropathy, kidney disease, and retinopathy [1]. It results in movement restrictions leading to compromised quality of life. Although it has been discussed extensively in previous pieces of literature, there is a paucity regarding its presentation at current times. Here, we present a unique case of extensive LJM involving both hands and feet in a type 1 diabetes mellitus (T1DM) patient.

Case presentation

A 25-year-old boy with T1DM had presented with progressive flexion deformity of both hands and feet for the last 6 years. He was diagnosed at 14 months of age and has started on insulin since then. He had very poor glycemic control from childhood on twice daily pre-mix insulins, and his current glycated hemoglobin (HbA1c) was 10.1%. He used to administer insulin in his thighs and did not rotate properly. None of his family members had diabetes nor did they have any known chronic rheumatological or joint-bone disorders. Initially, the little fingers of both hands developed flexion deformity, followed by the involvement of the other fingers and toes. There was no history of any trauma, pain, redness, or morning stiffness.

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Examination findings and investigations

His body mass index was 21.9 kg/m^2. Lipodystrophy was found in both the thighs at the injection sites. The hands revealed symmetrical contractures of the metacarpo-phalangeal and inter-phalangeal joints of all the fingers (Fig. 1). Similarly, metatarso-phalangeal and inter-phalangeal joints of toes were also involved (Fig. 2). The "prayer sign" (incomplete approximation of all the fingers of upper limbs) (Fig. 3) as well as "table-top sign" (inability to lay all the fingers in a flat table) were positive in this patient. Large joints of both the limbs and the axial skeleton were not involved. The skin over the hand was thick, tight, and waxy. All were suggestive of advanced LJM and subsequently classified as stage III as per the Brink-Starkman classification [1]. Neurological examinations revealed distal symmetric sensory polyneuropathy without any motor involvement. Ophthalmological examination revealed bilateral moderate non-proliferative diabetic retinopathy in both eyes. His 24-hour urinary protein excretion was 456 mg.

Management

The patient was started on a basal-bolus insulin regimen and was given adequate diabetes education. He was started on palmar-stretching exercises to maintain his hand's range of motion. The patient is currently following up in our outpatient department with a relative improvement after 6 months of initial contact.

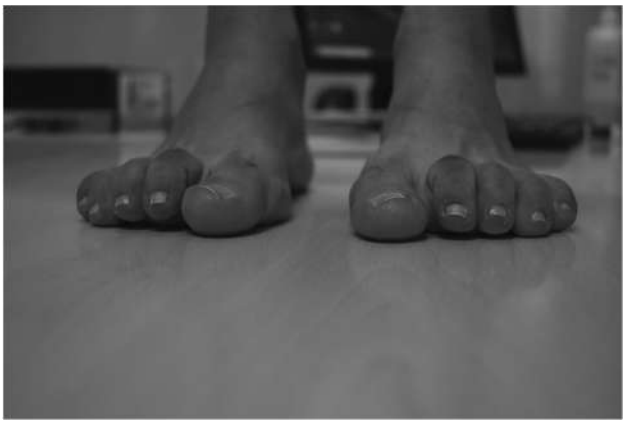

Fig. 2 Patient's feet showing symmetrical flexor contractures in the inter-phalangeal joints and hyper-extension in the metatarso-phalangeal joints

Discussion

The description of LJM in diabetes dates way back to 1970 by Rosenbloom A. The main underlying factor has been poor glycemic control. Similarly, our patient also had very poor glycemic control, which mostly contributed to his parent's lack of insulin education. It has been described as early as 7 months after diagnosis and as late as after 30 years of diagnosis [2]. LJM is seen in about 9 to 66% of patients with T1DM.

The main phenotypical feature is restriction in the flexion movements, which is mostly described in the hands. Its chief pathogenesis has been abnormal cross-linking of collagen in the dermis. The biopsy studies have shown additional thickening

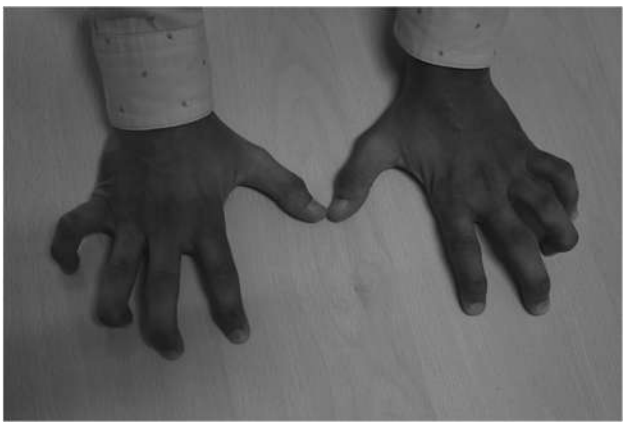

Fig. 1 Patient's hands showing extensive flexion deformities in inter-phalangeal and metacarpo-phalangeal joints

Fig. 3 Patient's fingers are unable to approximate due to fixed flexion deformity: "prayer sign"

of the epidermis also with the loss of skin appendages [3]. The skin thickening in scleroderma involves both the large (> 60 nm) and small (< 60 nm) dermal collagen fibers, whereas only small fibers are involved in LJM [4]. "Table-top" sign and "prayer sign" are both easy clinical tools to detect LJM, where the "prayer" sign is reported to be more sensitive [5]. Patients can have thick and waxy skin, which can be found in 70% and 100% of patients with mild and severe LJM, respectively [6].

The LJM is consistently associated with microvascular complications. Retinopathy was reported in 52.4% of patients compared to 12.3% in patients without LJM in an Irish study [7]. The retinopathy risk increases about 2.5 times in LJM patients compared to non-LJM diabetes. The risk of nephropathy and neuropathy goes up to 3 to fivefold in patients with LJM. These patients have typically reduced nerve velocity in the median and ulnar nerve with reduced vibratory sensation in all 4 limbs. Detecting the earliest LJM changes in T1DM can alert us to the possible development of these microvascular complications and can be quite rewarding for clinicians to prevent them [8].

The differential diagnosis in such a case includes carpal tunnel syndrome, Dupuytren's contracture, stiff-hand syndrome, and scleroderma. The absence of any clinical signs of inflammation and normal inflammatory markers, lack of Raynaud's phenomenon, and negative auto-antibodies ruled out systemic sclerosis. LJM starts from the radial fingers and gradually involves the other fingers [9]. Women of more than 40 years of age mostly suffered from Dupuytren's contracture, where 3rd and 4th fingers are mostly involved. Flexor tenosynovitis mostly involves the 1st, 3rd, and 4th fingers with marked female preponderance. Carpal tunnel syndrome can involve all the fingers and is caused by median and ulnar nerve palsy [9]. Stiff-hand syndrome can present with calcified vessels and severe pain in the affected fingers. The absence of definite pain, in this case, virtually rules out all these possibilities. Such cases of advanced LJM in a T1DM generally present with growth failure. This patient had a height of 151 cm (mid-parental height being 165 cm). LJM patients typically have lower IGF-1 levels compared to age and sex-matched controls [10].

Severe LJM is regarded to be an irreversible disorder. Apart from intensive glycemic control and palmar-stretching, occupational therapy has been found to be helpful. Our patient did not have any occupational limitations as of now, so the former two therapeutic options are mostly stressed. Non-steroidal anti-inflammatory drugs, corticosteroids, and surgical intervention can be used in severe symptomatic cases [5].

Conclusion

The uniqueness behind this description lies in the advanced presentation of LJM involving both the upper and lower limbs. This case also illustrates the need for regular checks for musculoskeletal involvement in T1DM, which are frequently missed. Early detection of LJM can not only prevent microvascular complications but also can optimize the patient's physical abilities.

Acknowledgments The authors thank the patient and his parents for consenting to this medical case report.

Data Availability The datasets used and/or analyzed during the current case are available from the corresponding author on reasonable request.

Declarations

Ethics approval This article does not contain any use of animals or drugs by any of the authors.

Informed consent The patient signed informed consent regarding publishing his data and photographs.

Conflict of interest The authors declare no competing interests.

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ORIGINAL ARTICLE

Silencing of DIRAS3 improves the proliferation and insulin secretion of palmitic acid-treated pancreatic β-cells through regulating PI3K/AKT signaling

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Abstract

Background Type-2 diabetes mellitus is a metabolic disorder characterised by hyperglycemia and insulin resistance. This study aims to explore the role and mechanism of DIRAS family GTPase 3 (DIRAS3) in mediating pancreatic β-cell death and insulin secretion.

Materials and Methods A bioinformatic analysis of the GSE118230 and GSE150281 datasets was performed to screen differentially expressed genes. The pancreatic β-cell lines, INS-1 and MIN6, were treated with palmitic acid (PA) to mimic the cell models of type-2 diabetes mellitus. CCK-8 assay, 5-ethynyl-2'-deoxyuridine staining, flow cytometry, enzyme-linked immunoassay, immunofluorescence, qRT-PCR, and western immunoblotting were conducted to illustrate the role of DIRAS3 in the cell models.

Results Unlike in normal controls, DIRAS3 was highly expressed in PA-treated pancreatic β-cells in a dose- and time-dependent manner. Moreover, the silencing of DIRAS3 in the INS-1 cells attenuated PA-induced cell loss by improving cell proliferation and inhibiting apoptosis and prevented the PA-induced impairment of insulin secretion. Consistently, the overexpression of DIRAS3 in the MIN6 cells accelerated PA-induced cell loss and impaired insulin secretion. A Gene Set Enrichment Analysis predicted that phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) was a downstream signalling pathway of DIRAS3, as the inhibitory effects of DIRAS3 on the activation of the PI3K/AKT signalling pathway were confirmed in the INS-1 and MIN6 cells. Moreover, the PI3K inhibitor, LY294002, effectively reversed the protective effects of DIRAS3 silencing on the INS-1 cells.

Conclusion DIRAS3 was highly expressed in the cell models of type-2 diabetes mellitus, contributing to PA-induced cell death and impaired insulin secretion in pancreatic β-cells through the inhibition of the PI3K/AKT signalling pathway.

Keywords DIRAS3 · diabetes mellitus · palmitic acid · pancreatic β · Cells · PI3K/AKT signalling

Highlights
1. DIRAS3 is highly expressed in cell models of diabetes mellitus;.
2. DIRAS3 inhibits the proliferation of palmitic acid-treated pancreatic β-cells;.
3. DIRAS3 induces apoptosis and insulin secretion impairment in pancreatic β-cells;.
4. Silencing of DIRAS3 protects pancreatic β-cells via regulating PI3K/AKT signalling.

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Introduction

Type-2 diabetes mellitus, also known as non-insulin-dependent diabetes mellitus, is a metabolic disorder characterised by hyperglycaemia and insulin resistance [1]. The International Diabetes Federation estimated that there will be more than 123 million patients with diabetes mellitus by 2035, with nearly 95% of whom having type-2 diabetes mellitus [2]. Currently, oral hypoglycaemics such as metformin hydrochloride, repaglinide, acarbose, and glimepiride are recommended for patients with type-2 diabetes mellitus [3]. Although these drugs always achieve satisfactory therapeutic goals, they still have several disadvantages which limit their therapeutic effect and patient compliance, including differential bioavailability, short half-life, and significant side

effects such as hypoglycaemia and weight gain [3]. Thus, further understanding of the pathogenesis of type-2 diabetes mellitus is required to develop novel antidiabetic drugs.

Phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signalling controls diverse cellular events in mammals, including cell proliferation, cell death, DNA repair, and tumourigenesis [4] and prevents cell apoptosis by inhibiting BAD phosphorylation and caspase cleavage [5]. In addition, activated AKT regulates c-Myc, cyclin D, and GSK to promote cell proliferation [6, 7]. The critical role of the PI3K/AKT signalling pathway in human diseases, including neurodegenerative diseases [8–10], ischemic stroke [11], acute lung injury [12], and cancer [13], have gained increasing interest. This pathway is responsible for maintaining normal metabolism; thus, its imbalance results in the development of type-2 diabetes mellitus [6]. Moreover, the activation of the PI3K/AKT signalling pathway in pancreatic β-cells increases insulin secretion and promotes cell proliferation [14, 15]; therefore, the effective inhibition of PI3K has the potential to alleviate insulin resistance and treat type-2 diabetes mellitus [6].

DIRAS family GTPase 3 (DIRAS3, also known as ARHI) is a 26 kDa GTP-binding protein that has been identified as an anticancer gene in head and neck squamous cell carcinoma [16], breast cancer [17], and pancreatic cancer [18]. The either blocked or reduced expression of DIRAS3 leads to cancer cell excessive proliferation and cell death inhibition [19]. In addition, DIRAS3-induced cell death in ovarian cancer cells is associated with a reduced PI3K and AKT activity [20, 21]. Currently, studies on DIRAS3 are limited to cancer research. However, the role of DIRAS3 in other human diseases including diabetes mellitus remains unclear; thus, this study aims to reveal the biological role of DIRAS3 in type-2 diabetes mellitus. Accordingly, pancreatic β-cell lines were treated with palmitic acid (PA) to mimic a disease cell model. We investigated the effects of DIRAS3 on cell proliferation, apoptosis, and insulin secretion and determined the effects of the regulation of DIRAS3 on PI3K/AKT signalling pathway.

Materials and methods

Bioinformatic analysis

The GSE118230 and GSE150281 datasets from the GEO public database (http://www.ncbi.nlm.nih.gov/geo/) were used to screen differentially expressed genes in type-2 diabetes mellitus. The GSE118230 dataset includes 30 samples, five control and 25 PA-treated samples (0.5 mM palmitate for 4 h, 12 h, 1 d, 2 d, and 7 d, respectively). The GSE150281 dataset comprises gene information from the pancreatic islets of diabetes-prone New Zealand obese mice. The pancreatic islets were collected from 18-week-old and 39-week-old mice which were fed with a high-fat diet and an additional carbohydrate-rich diet. Genes, differentially expressed between the GSE118230 and GSE150281 datasets, were screened using the R limma package. The Gene Set Enrichment Analysis (GSEA) software was used to select the DIRAS3-related signalling pathways. A GO term function annotation and a KEGG pathway analysis were performed using the ClusterProfiler package in R language.

Cell culture

β-TC-6, INS-1, RIN-m5F, and MIN6 cell lines were purchased from Procell Biological Cell Company (Wuhan, China). The β-TC-6 cells were cultured in Dulbecco's Modified Eagle's medium (Gibco, USA) which was supplemented with 15% heat-inactivated fetal bovine serum (FBS) (Hyclone, USA). The RIN-m5F cells were cultured in Roswell Park Memorial Institute (RPMI)-1640 medium (Gibco, USA) which was supplemented with 10% FBS. The INS-1 and MIN6 cells were cultured in RPMI-1640 medium with 10% FBS and 0.05 mM β-mercaptoethanol (Sigma-Aldrich, USA). The cells were cultured at 37 °C in a 5%-CO_2 environment.

PA, with a > 99% purity, purchased from Sigma-Aldrich (USA) was dissolved in 90% ethanol, heated to 60 °C, and diluted in RPMI-1640 medium as previously reported [22]. An equal amount of ethanol in the culture medium, at a final concentration of 0.2%, was used as the control. The INS-1 and MIN6 cells were treated with 0, 50, 100, 200, or 400 μM PA for 0, 12, 24, or 48 h. At a final concentration of 50 Mm, the PI3K inhibitor, LY294002, (MedChemExpress, USA) was used to treat the cells for 24 h.

Cell transfection

Regarding INS-1 cell transfection, cells at 70–80% confluence were transfected with 100 nM rat siRNAs specific against DIRAS3 (sense, 5'-CAAAGUUAUCCAACG GUAAAC-3'; antisense, 5'-UUACCGUUGGAUAACU UUGUG-3') or the negative control siRNA (siNC). Regarding MIN6 cell transfection, 2-μg mouse pcDIRAS3 or empty pcDNA3.1 plasmid were used. Transfection was performed using Lipofectamine 2000 (Invitrogen) according to the manufacturer's instructions. Briefly, Lipofectamine® 2000 Reagent and DNA were diluted in Opti-MEM® medium, were then mixed (1:1), and were used for cell transfection for 48 h at 37°C.

CCK-8 assay

Cell viability was analysed using a CCK-8 kit (Beyotime, China), a widely used colorimetric detection kit based

on WST-8. After transfection, the INS-1 and MIN6 cells were seeded in 96-well plates (5×10^3/well) and treated with 400 μM PA for 48 h. At the end of the treatment, the cells were treated with 10 μl/well CCK-8 reagent for 1 h at room temperature. The optical density was detected to beat 450 nm by using a microplate detector (PerkinElmer, Germany).

5-ethynyl-2′-deoxyuridine (EdU) staining

After transfection, the INS-1 and MIN6 cells in 96-well plates (5×10^3/well) were treated with 400 μM PA for 48 h. To detect cell proliferation, cells were stained with EdU reagent (50 μM/well, Beyotime) for 2 h at room temperature. Five randomly selected fields were photographed under a fluorescence microscope to calculate EdU-positive cell rate.

Flow cytometry

The transfected INS-1 and MIN6 cells in 6-well plates (5×10^5/well) were treated with 400 μM PA for 48 h. To detect cell apoptosis, 1×10^5 cells were stained using the Annexin V-FITC/PI Apoptosis Assay kit (Sangon Biotech, Shanghai, China). Apoptotic cells were analysed using a flow cytometer (BD Biosciences, USA).

Immunofluorescence

The transfected INS-1 and MIN6 cells were seeded in culture dishes with glass slides. After treating with 400 μM PA for 48 h, cells were washed thrice with phosphate buffer saline, fixed with 4% paraformaldehyde for 15 min, permeabilised with 0.5% Triton X-100 for 20 min, and stained with primary insulin antibody (#4590, dilution 1:100, Cell Signaling Technology, USA) at 4 ℃ overnight. After incubation with the secondary fluorescent antibody (1:500) along with 1 μg/ml DAPI for 1 h at room temperature, the slides were imaged under a fluorescence microscope..

Enzyme-linked immunoassay (ELISA)

Upon the completion of the designated treatment, the culture media of the INS-1 and MIN6 cells were collected. Insulin levels in the culture medium were analysed using ELISA kits (Cusabio, Wuhan, China) according to the manufacturer's instructions.

qRT-PCR

Total RNAs were extracted from the INS-1 and MIN6 cells using RNAiso Plus (TaKaRa, Dalian, China). cDNA was synthesised using a Reverse Transcription kit (Solarbio, Shanghai, China). PCR was performed using SYBR Green (Solarbio) with the following primers: Rattus norvegicus DIRAS3: forward, 5'-ATTGGGACCCTCTCTGACGA-3', reverse, 5'-CCTGAGCCGTCAGTACTT GG-3'; Rattus norvegicus β-actin: forward, 5'-CCGCGAGTACAACCTTCT TG-3', reverse, 5'-CGTCATCCATGGCGAACTGG-3'; Mus musculus DIRAS3: forward, 5'-CCCGTTCCTGGAAAT CACGA-3', reverse, 5'-TCCCGTCCAGTATCCCCTTT-3'; and Mus musculus β-actin: forward, 5'-CCAGCCTTCCTT CTTGGGTAT-3', reverse, 5'-GGGTGTAAAACGCAGCTC AG-3'. The thermocycling conditions were 94 ˚C for 30 s, followed by 40 cycles of 50–63 ˚C for 30 s, 72 ˚C for 1 min, and finally 72 ˚C for 10 min.

Western blot

Total proteins in the INS-1 and MIN6 cells were isolated using RIPA buffer (Solarbio) with 0.1 mM of the protease inhibitor, phenylmethylsulfonyl fluoride (PMSF; MedChemExpress, NJ, USA). After centrifugation at 12,000 rpm at 4 ℃ for 5 min, protein concentration was analysed using BCA Protein Assay kit (Solarbio). A sample of 50 μg protein was loaded onto 10%–12% SDS-PAGE gels (40 V for 4 h), and the separated proteins were transferred onto PVDF membranes. The membranes were blocked in 5% BSA blocking buffer for 1 h at room temperature, incubated with primary antibodies against DIRAS3 (ab107051, Abcam), Cyclin D1 (ab226977, Abcam), Cyclin E1 (ab133266, Abcam), Bax (50599–2-Ig, Proteintech), Bcl-2 (3498 T, Cell Signaling Technology), Cleaved caspase-3 (ab2302, Abcam), p-PI3K (ab278545, Abcam), PI3K (4257 T, Cell Signaling Technology), p-AKT (4060 T, Cell Signaling Technology), and AKT (4691 T, Cell Signaling Technology) and then incubated with the secondary anti-rabbit antibody (ab205718, Abcam). Target protein bands were developed using the ECL chemiluminescence kit (Beyotime, China).

Statistical analysis

All experiments were repeated thrice in triplicate and are shown as the mean ± SD. A Student's t-test was performed for two-group comparison, and one-way ANOVA was performed for multiple-group comparisons. Statistical significance was set at a p-value of < 0.05.

Results

DIRAS3 is highly expressed in the cell models of diabetes mellitus

The differentially upregulated genes between the GSE118230 and GSE150281 datasets were screened, and three overlapping genes were identified: SLC6A17,

DIRAS3, and EFR3B (Fig. 1A). SLC6A17 is exclusively expressed in the brain and acts as a transporter for neutral amino acids [23]. EFR3B is another overlapping gene with an unknown biological role in mammals. The role of DIRAS3 in various cancers has been revealed, particularly in the regulation of cancer cell proliferation and apoptosis [16, 24]. Thus, DIRAS3 was selected for the following investigations. In the GSE118230 dataset, DIRAS3 was highly expressed in the PA-treated human islet cells ($p < 0.05$; Fig. 1B). To confirm the dysregulation of DIRAS3 in the cell models of diabetes mellitus, the expression of DIRAS3 was detected in several pancreatic β-cell lines. qRT-PCR data showed that DIRAS3 was basally expressed in the β-TC-6, INS-1, RIN-m5F, and MIN6 cells (Fig. 1C). Among these cell lines, INS-1 and MIN6 exhibited the highest and lowest DIRAS3 levels, respectively. The treatment of the INS-1 and MIN6 cells with various doses of PA (50, 100, 200, and 400 μM) for 48 h increased the mRNA and protein levels of DIRAS3 ($p < 0.05$; Fig. 1D-F). In addition, the treatment of the INS-1 and MIN6 cells with 400 μM PA for gradually increased time (12, 24, and 48 h) significantly increased DIRAS3 expression at both mRNA and protein levels ($p < 0.05$; Fig. 1G-I). PA treatment increased DIRAS3 expression in a dose- and time-dependent manner.

DIRAS3 inhibits the proliferation of PA-treated pancreatic β-cells

Given that DIRAS3 has high basal expression in the INS-1 cells, siRNA specific against DIRAS3 was transfected into the INS-1 cells to reveal the biological function of DIRAS3. Unlike for siNCs, the INS-1 cells transfected with siDIRAS3 showed much lower DIRAS3 expression ($p < 0.05$; Fig. 2A-B). The treatment of the INS-1 cells with 400 μM PA significantly inhibited cell viability and the EdU-positive cell rate ($p < 0.05$; Fig. 2C-D). However, unlike for siNC, the transfection of the INS-1 cells with siDIRAS3 significantly attenuated the PA-induced decrease in cell viability

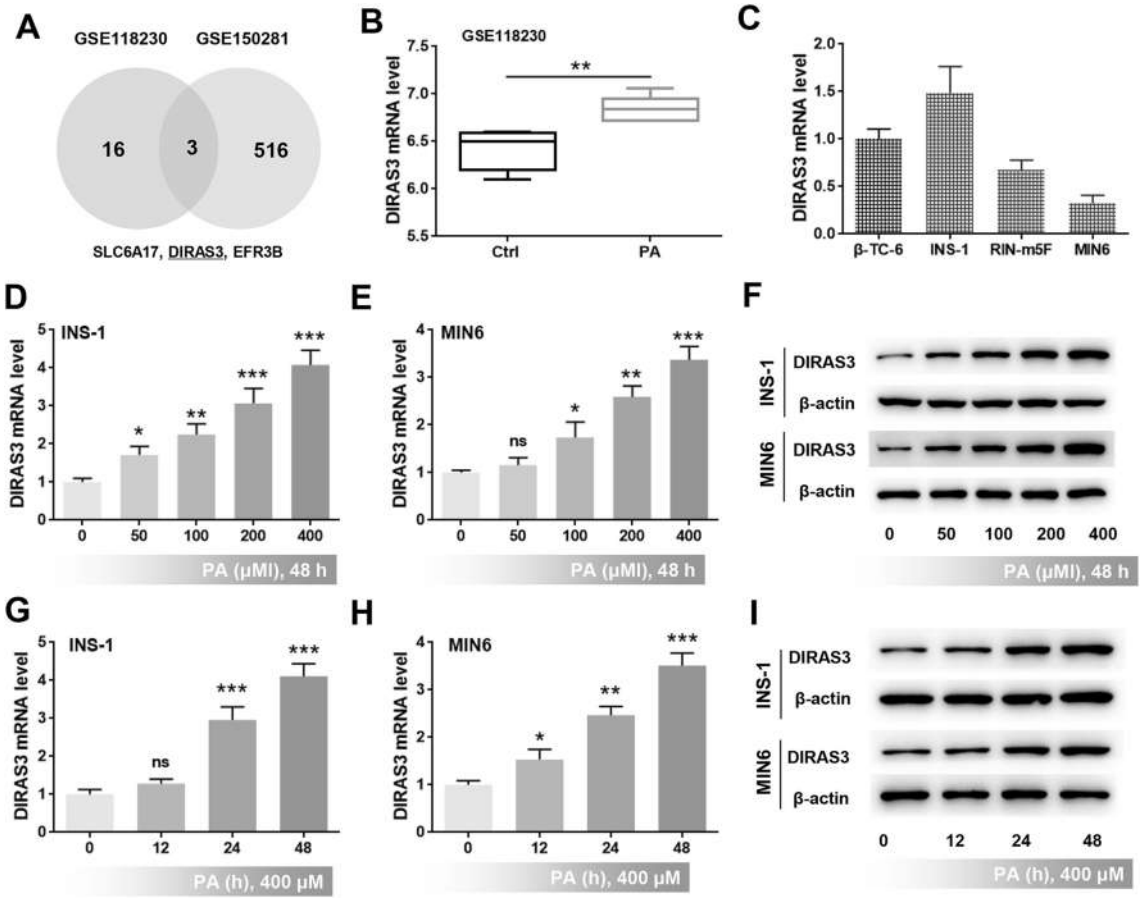

Fig. 1 Expression of DIRAS3 in cell models of diabetes mellitus. **A** Overlapping analysis of GSE118230 and GSE150281 datasets. **B** Expression of DIRAS3 in GSE118230 dataset. **C** mRNA level of DIRAS3 in several pancreatic β-cell lines was detected by qRT-PCR. **D-F** INS-1 and MIN6 cells were treated with various doses of PA (50, 100, 200, and 400 μM) for 48 h. Expression of DIRAS3 was detected by qRT-PCR and immunoblotting. **G-I** INS-1 and MIN6 cells were treated with 400 μM PA for gradually increased time (12, 24, and 48 h). Expression of DIRAS3 was detected by qRT-PCR and immunoblotting. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$

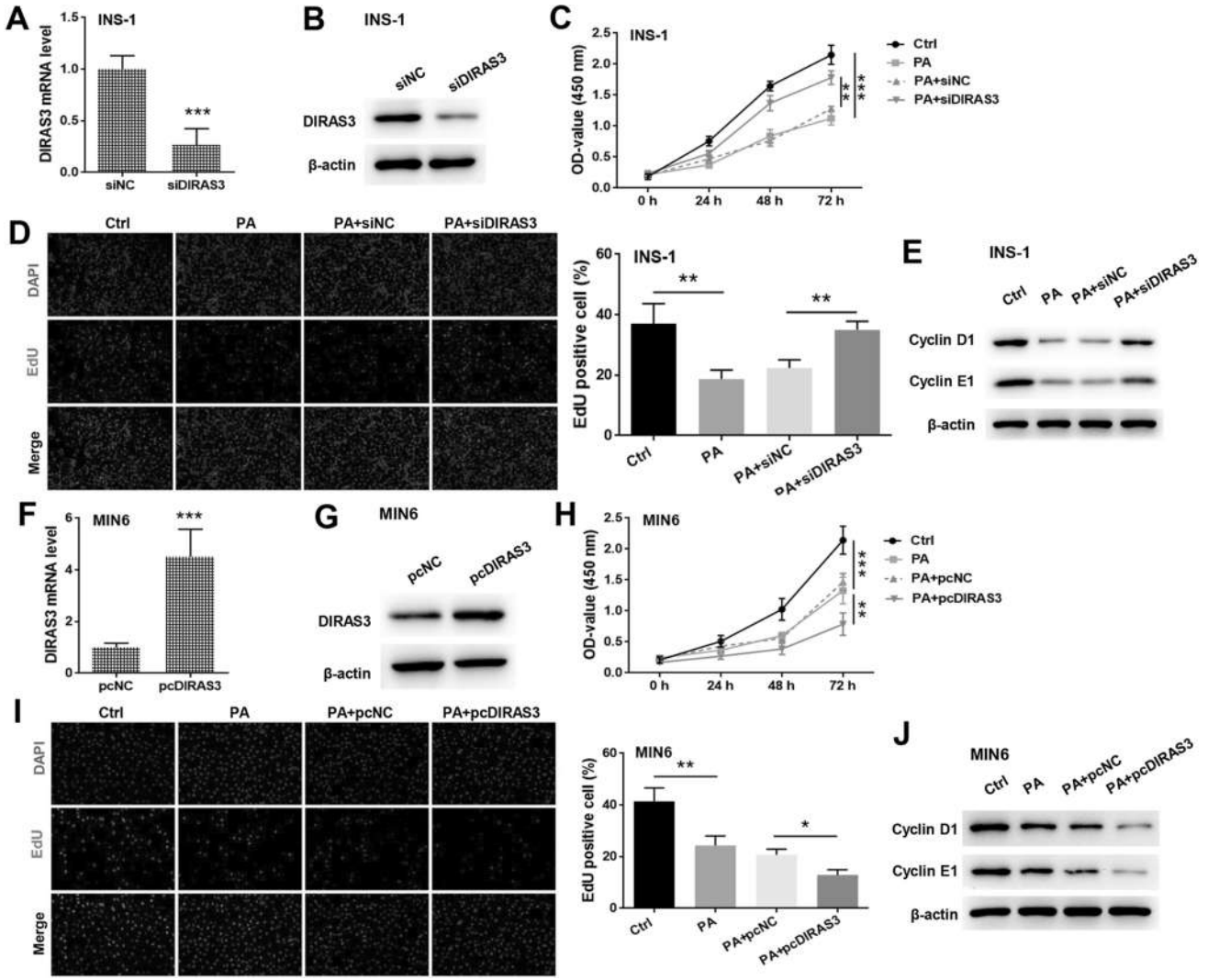

Fig. 2 Effects of DIRAS3 on pancreatic β-cell proliferation. **A**-**B** INS-1 cells were transfected with siNC or siDIRAS3. Expression of DIRAS3 was detected by qRT-PCR and immunoblotting. **C**-**D** Viability and proliferation of INS-1 cells were detected by CCK-8 and EdU assay respectively, after the designated transfection and PA treatment. **E** Expression of Cyclin D1 and Cyclin E1 was detected by immunoblotting, after the designated transfection and PA treatment. **F**-**G** MIN6 cells were transfected with pcNC or pcDIRAS3. Expression of DIRAS3 was detected by qRT-PCR and immunoblotting. **H**-**I** Viability and proliferation of MIN6 cells were detected by CCK-8 and EdU assay respectively, after the designated transfection and PA treatment. **J** Expression of Cyclin D1 and Cyclin E1 was detected by immunoblotting, after the designated transfection and PA treatment. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$

and EdU-positive cell rate ($p < 0.05$). Consistent with these findings, the downregulation of cyclin D1 and E1 in PA-treated INS-1 cells was attenuated by siDIRAS3 rather than by siNC (Fig. 2E).

To further confirm the regulatory effects of DIRAS3 on the proliferation of pancreatic β-cells, a DIRAS3 overexpression vector was transfected into the MIN6 cells, a cell line with low basal expression. The transfection of the MIN6 cells with pcDIRAS3 remarkably increased the expression of DIRAS3, in contrast to cells transfected with pcNC ($p < 0.05$; Fig. 2F-G). The treatment of the MIN6 cells with 400 μM PA significantly reduced cell viability and EdU-positive cell rate ($p < 0.05$; Fig. 2H-I). The transfection of the MIN6 cells with pcDIRAS3 further accelerated the inhibitory effects of PA on cell viability and EdU-positive cell rate, in contrast to transfection with pcNC ($p < 0.05$). Additionally, the transfection of the MIN6 cells with pcDIRAS3 further downregulated the PA-induced expression of cyclin D1 and cyclin E1, whereas pcNC had no visible effects (Fig. 2J). Collectively, these data suggested that DIRAS3 might contribute to the PA-induced impairment of pancreatic-cell proliferation.

DIRAS3 induces apoptosis and insulin secretion impairment in pancreatic β-cells

The role of DIRAS3 in mediating pancreatic β-cell apoptosis and impairing insulin secretion were then investigated. As shown in Fig. 3A, treating the INS-1 cells with 400 μM PA induced a significant increase in cell apoptosis ($p < 0.05$). The transfection of the INS-1 cells with siDIRAS3 significantly attenuated PA-induced apoptosis, unlike with siNC ($p < 0.05$). Consistently, PA treatment remarkably upregulated Bax and cleaved caspase-3 and downregulated Bcl-2, whereas the regulation of these proteins by PA was reversed by siDIRAS3 transfection rather than by siNC (Fig. 3B). Immunofluorescence staining showed that PA treatment impaired insulin secretion in the INS-1 cells (Fig. 3C). Unlike for siNC, the transfection of the INS-1 cells with siDIRAS3 markedly attenuated PA-induced insulin secretion impairment. In addition, ELISA data (Fig. 3D) showed that the decreased insulin levels induced by PA

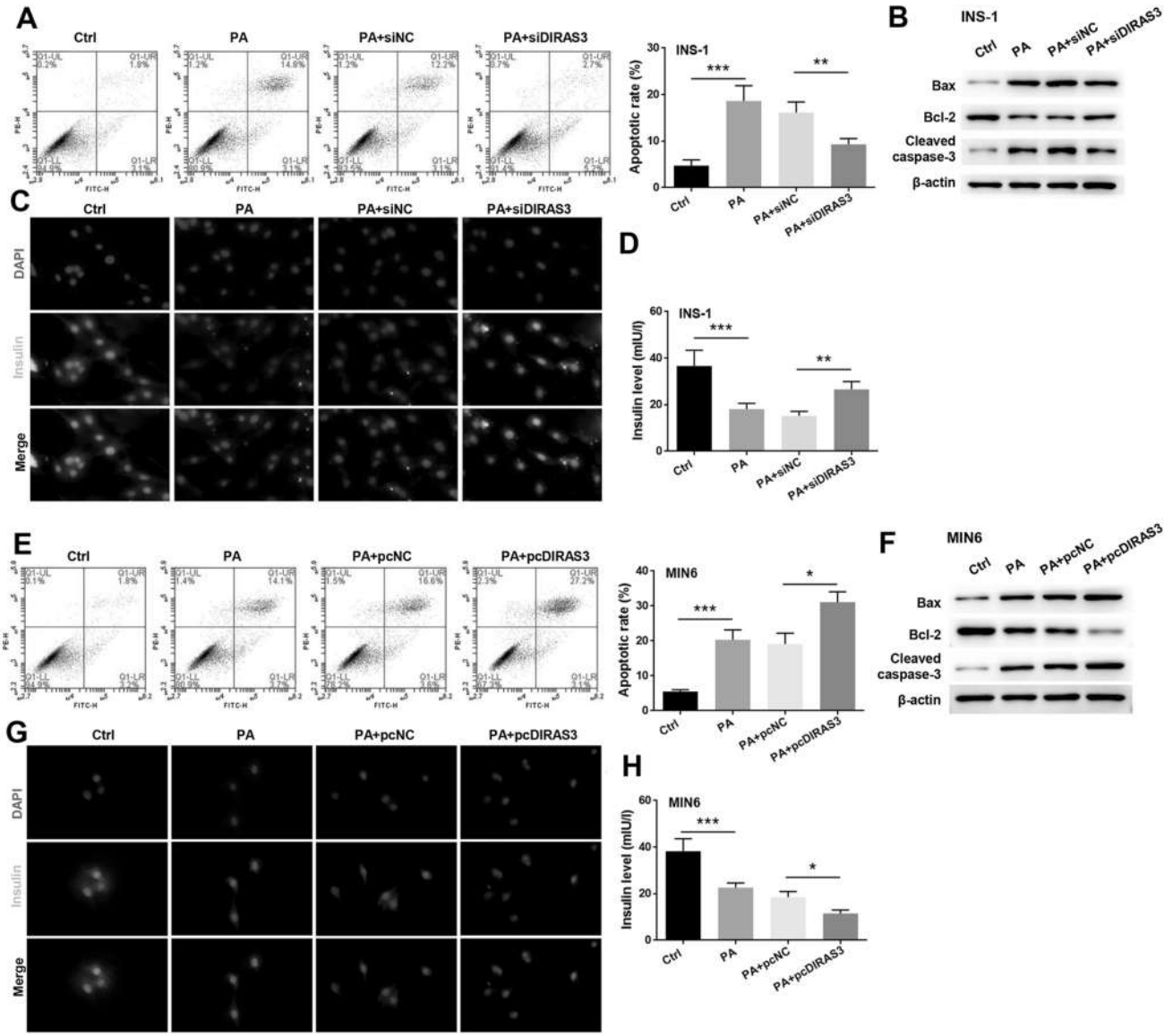

Fig. 3 Effects of DIRAS3 on pancreatic β-cell apoptosis and insulin secretion. **A**-**B** INS-1 cell apoptosis and the expression of apoptosis-related proteins were detected by flow cytometry and immunoblotting respectively, after the designated transfection and PA treatment. **C**-**D** Insulin secretion of INS-1 cells was detected by immunofluorescence and ELISA respectively, after the designated transfection and PA treatment. **E**–**F** MIN6 cell apoptosis and the expression of apoptosis-related proteins were detected by flow cytometry and immunoblotting respectively, after the designated transfection and PA treatment. **G**-**H** Insulin secretion of MIN6 cells was detected by immunofluorescence and ELISA respectively, after the designated transfection and PA treatment. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$

treatment were attenuated by siDIRAS3 ($p < 0.05$), but not by siNC.

Treating the MIN6 cells with 400 μM PA significantly induced apoptosis ($p < 0.05$; Fig. 3E). Unlike with pcNC, the transfection of the MIN6 cells with pcDIRAS3 further increased apoptosis-induced by PA ($p < 0.05$). The expression of Bax and cleaved caspase-3 was upregulated, whereas that of Bcl-2 was downregulated by PA treatment (Fig. 3F). The effect of PA on the protein levels was further accelerated by pcDIRAS3 rather than by pcNC (Fig. 3F). Immunofluorescence staining and ELISA results showed that the effects of PA on insulin secretion in the MIN6 cells were further impaired by pcDIRAS3 rather than by pcNC ($p < 0.05$; Fig. 3G-H). These data suggested that DIRAS3 might contribute to pancreatic β-cell apoptosis and impairment of insulin secretion induced by PA.

DIRAS3 inhibits PI3K/AKT signalling in pancreatic β-cells

Moreover, the effects of DIRAS3 on pancreatic β-cells were investigated. A GSEA analysis revealed several biological processes and pathways (Fig. 4A). Given that the PI3K/AKT signalling pathway has the third highest enrichment score and is critical in regulating cell proliferation and apoptosis [7], it was selected for the following experiments. In the INS-1 cells, siDIRAS3 induced the activation of PI3K/AKT signalling, as the levels of phosphorylated PI3K and AKT

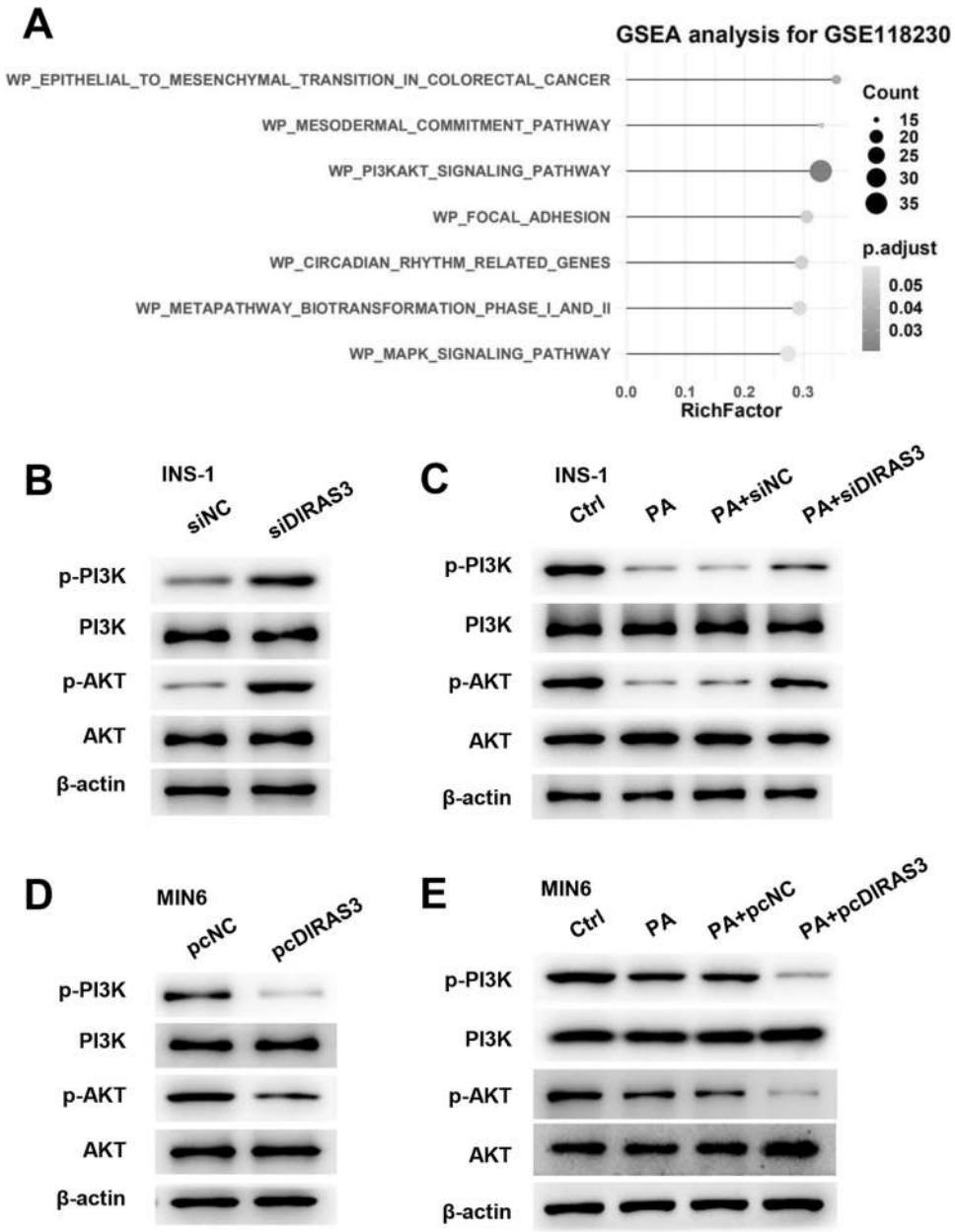

Fig. 4 Effects of DIRAS3 on regulating PI3K/AKT signalling in pancreatic β-cells. **A** GSEA analysis for screening signalling pathways that can be altered by DIRAS3. **B** Expression of PI3K and AKT was detected by immunoblotting in INS-1 cells, after transfection with siNC or siDIRAS3. **C** Immunoblotting detection of PI3K and AKT expression in INS-1 cells, following the designated transfection and PA treatment. **D** Expression of PI3K and AKT was detected by immunoblotting in MIN6 cells, after transfection with pcNC or pcDIRAS3. **E** Immunoblotting detection of PI3K and AKT expression in MIN6 cells, following the designated transfection and PA treatment

were remarkably upregulated (Fig. 4B). The treatment of the INS-1 cells with PA deactivated PI3K and AKT, and these effects were attenuated by siDIRAS3 treatment (Fig. 4C). The transfection of the MIN6 cells with pcDIRAS3 inhibited the activation of PI3K/AKT signalling, as evidenced by the downregulation of phospho-PI3K and -AKT (Fig. 4D). The downregulation of phospho-PI3K and -AKT induced by PA treatment was further accelerated by pcDIRAS3 in the MIN6 cells (Fig. 4E). These results suggested that PI3K/AKT is a downstream signalling pathway of DIRAS3 that mediates PA-induced pancreatic β-cells.

Silencing of DIRAS3 protects pancreatic β-cells through regulating PI3K/AKT signalling

To confirm the above mentioned hypothesis, the INS-1 cells were transfected with siNC or siDIRAS3 and treated with PA with or without the PI3K inhibitor, LY294002. As shown in Fig. 5A, siDIRAS3 significantly increased the rate of EdU-positive INS-1 cells, which was reversed by the addition of LY294002 ($p < 0.05$). siDIRAS3 transfection significantly inhibited PA-induced apoptosis, and this inhibitory effect was reversed by LY294002 treatment ($p < 0.05$; Fig. 5B).

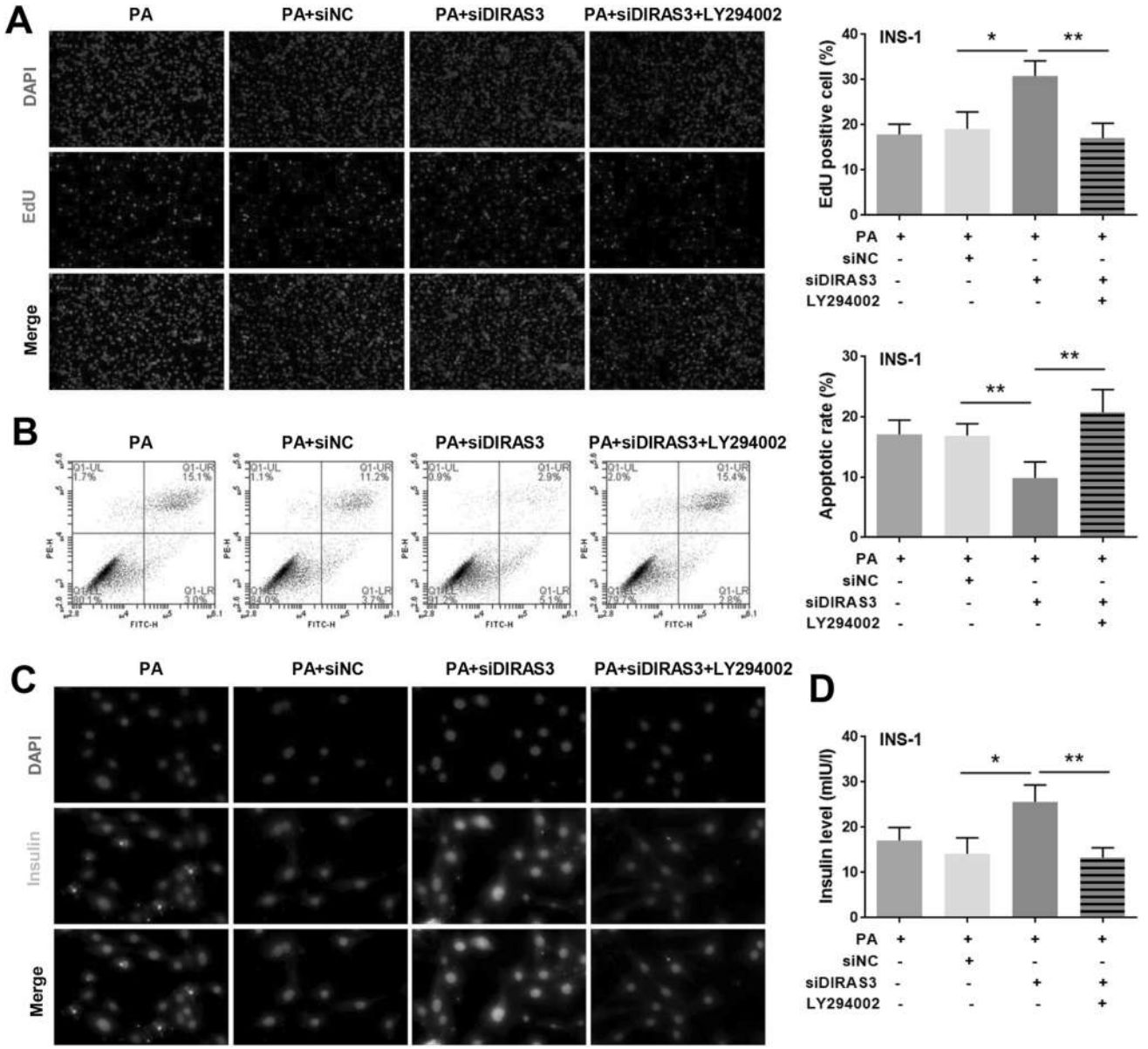

Fig. 5 Effects of DIRAS3 on pancreatic β-cells via regulating PI3K/AKT signalling. **A** The proliferation of INS-1 cells was detected by EdU assay, following the designated transfection and PA treatment with or without a PI3K inhibitor LY294002. **B** Apoptosis of INS-1 cells was detected by flow cytometry. **C**-**D** Insulin secretion of INS-1 cells was detected by immunofluorescence and ELISA, respectively. *, $p < 0.05$; **, $p < 0.01$

In addition, the protective effects of siDIRAS3 on insulin secretion were reversed by LY294002 treatment ($p < 0.05$; Fig. 5C-D). These data suggested that DIRAS3 silencing protected pancreatic β-cells against PA-induced injury, possibly through the activation of PI3K/AKT signalling.

Discussion

Type-2 diabetes mellitus is characterised by insulin resistance, which leads to the loss of pancreatic β-cells and the impairment of β-cell function [25]. Although the pathogenesis of insulin resistance remains unclear, free fatty acids are thought to be involved [26]. Circulating free fatty acids that depend on dietary intake can cause diacylglycerol generation, proinflammatory cytokine release, and oxidative stress, ultimately accounting for insulin resistance in type-2 diabetes mellitus [27]. As a representative free fatty acid, PA is commonly used as a stimulus to mimic the cell models of type-2 diabetes mellitus [28]. According to several previous reports [29, 30], 400 μM PA was used to treat pancreatic β-cell lines, INS-1 and MIN6. As a result, PA treatment induced a significant loss of the INS-1 and MIN6 cells, probably caused by cell apoptosis. In addition, PA treatment impaired insulin secretion in the INS-1 and MIN6 cells and significantly upregulated DIRAS3 expression. DIRAS3 silencing in the INS-1 cells attenuated PA-induced cell death and impaired insulin secretion. Consistently, the overexpression of DIRAS3 in the MIN6 cells accelerated PA-induced cell damage. The effects of DIRAS3 on PA-induced pancreatic β-cell death and dysfunction were possibly mediated through the regulation of PI3K/AKT signalling.

DIRAS3 is an imprinted gene that is associated with growth suppression. Therefore, it has increasingly as acted as a tumour suppressor in various human cancers [16–18]. For instance, the overexpression of DIRAS3 in head and neck squamous cell carcinoma cells downregulates c-Myc, cyclin D1, and Bcl-2 to inhibit cell growth and promote apoptosis [16]. The overexpression of DIRAS3 in ovarian cancer cells induces autophagy-related cell death to control cancer cell growth [31]. DIRAS3 enhances the sensitivity of ovarian cancer cells to cisplatin and induces apoptosis through the activation of caspase-3 and poly (ADP-ribose) polymerase [32]. In addition, a previous study suggested that DIRAS3 may be a potential target for diabetic retinopathy treatment and diagnosis [33]. The epigenetic silencing of DIRAS3 inhibits high glucose-induced cardiomyocyte autophagy which is beneficial for treating diabetic cardiomyopathy [34]. In this study, we investigated the pathogenic role of DIRAS3 in type-2 diabetes mellitus. An overlapping analysis of the GSE118230 and GSE150281 datasets identified DIRAS3 as a differentially expressed gene between normal and diabetes mellitus models. The significant upregulation of DIRAS3 was then confirmed in the cell models of type-2 diabetes mellitus. Further *in vitro* studies suggested that the highly expressed DIRAS3 in pancreatic β-cell in response to PA treatment may contribute to the pathogenesis of type-2 diabetes mellitus. DIRAS3 is involved in PA-induced cell loss, apoptosis, and impaired insulin secretion impairment.

The PI3K/AKT pathway is a well-known signalling pathway that participates in the regulation of cell survival and death [4]. Thus the dysregulation of PI3K/AKT signalling pathway is considered to be one of the mechanisms underlying the pathogenesis of type-2 diabetes mellitus [6]. Targeted therapies or drugs that activate the PI3K/AKT signalling pathway may be beneficial in preventing insulin resistance and type-2 diabetes mellitus [35, 36]. The regulation of DIRAS3 and PI3K/AKT has been studied in human cancers [37]. For example, DIRAS3 exerts tumour-suppressive effects on ovarian cancer cells by inhibiting the PI3K signalling pathway [21]. DIRAS3 induced apoptosis in head and neck squamous cell carcinoma cells by inhibiting AKT phosphorylation [16]. The overexpression of DIRAS3 inhibited pancreatic cancer cell proliferation and induced G1 cell cycle arrest by modulating the PI3K/AKT signalling pathway, which was identified as a downstream signalling of DIRAS3-mediated cell damage in pancreatic β-cells in this study. The overexpression of DIRAS3 in pancreatic β-cells repressed PI3K and AKT activity to accelerate PA-induced cell death and insulin secretion impairment.

Conclusion

In conclusion, DIRAS3 was highly expressed in the cell models of type-2 diabetes mellitus. High DIRAS3 expression contributes to PA-induced cell death and impaired insulin secretion in pancreatic β-cells. DIRAS3 exerts its effects possibly through the inhibition of the PI3K/AKT signalling pathway. This study provided an *in vitro* evidence that DIRAS3 is a potential therapeutic option for the treatment of insulin resistance and type-2 diabetes mellitus.

Author contributions Ying Li designed the study; Ying Li, Shan Gao and Ying Yang performed the research; Gang Yin analyzed data; Gang Yin wrote the paper. All authors have read and approved the manuscript.

Data availability The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and Consent to participate Not applicable.

Consent for publication Not applicable.

Competing Interests No conflicts and interests were involved.

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ORIGINAL ARTICLE

Impact of the supplementation of melatonin on oxidative stress marker and serum endothelin-1 in patients with metabolic syndrome

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Abstract

Objective Metabolic syndrome (MetS) is characterized by the cluster of risk factors associated with diabetes and cardiovascular diseases. Given the influential role of oxidative stress (OxS) in the pathogenesis of MetS and the antioxidant properties of melatonin, our study aims to investigate the impact of melatonin supplementation on OxS biomarkers and serum endothelin-1 (ET-1) levels in patients diagnosed with MetS.

Methods This double-blind, placebo-controlled, randomized clinical trial involved male and female adult participants with MetS. Subjects in the melatonin and control groups were administered 6 mg/day of encapsulated powdered melatonin or placebo (wheat flour), respectively, over a 12-week period. We evaluated serum levels of malondialdehyde (MDA), superoxide dismutase (SOD) activity, and ET-1 in MetS patients, both pre- and post-intervention.

Results Melatonin supplementation significantly decreased serum ET-1 level (1.55 ± 0.24 pg/ml vs. 0.808 ± 0.18 pg/ml; $p = 0.04$) and MDA (1.326 ± 0.05 μM vs. 1.134 ± 0.05 μM; $p = 0.021$) in the melatonin group relative to baseline values. Additionally, SOD activity displayed a significant increase (23.64 ± 2.77 U/ml vs. 41.35 ± 1.22 U/ml; $p = 0.0001$) in the melatonin group when compared to baseline.

Conclusion Our research indicates that 12 weeks of melatonin supplementation in MetS patients leads to a significant reduction in serum ET-1 and MDA levels, alongside an increase in SOD activity levels relative to baseline. However, further comprehensive and well-structured randomized controlled trials are essential for establishing the effects of melatonin supplementation on OxS biomarkers in diverse age demographics.

Keywords Cardiovascular diseases · Metabolic syndrome · Endothelin-1 · Melatonin

Introduction

Metabolic syndrome (MetS) is a condition characterized by the simultaneous occurrence of various metabolic disorders, which can increase the risk of diseases such as cardiovascular disease. Multiple definitions have been proposed for MetS [1], but its principal components generally include dyslipidemia, hypertension, hyperglycemia, and abdominal obesity [2]. The prevalence of MetS in the Iranian population exceeds the global estimated prevalence [3]. Studies have indicated a role for oxidative stress (OxS) in the pathogenesis of MetS [4], and a correlation between OxS and the number of MetS components has been identified [5]. OxS refers to an imbalance between oxidative and anti-oxidative systems, resulting from an overproduction of free radicals and reactive oxygen species (ROS), or impaired anti-oxidant systems [6]. The endogenous antioxidant defense system,

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composed of both non-enzymatic and enzymatic components, scavenges ROS. The enzymatic components include three main enzymes: glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) [7]. Lipids, particularly polyunsaturated fatty acids in the cell membrane, are major targets for free radical attacks. Malondialdehyde (MDA) is a final product of membrane fatty acids' peroxidation. Overproduction of ROS leads to an increase in MDA, a marker of OxS and antioxidant status [8].

Research has demonstrated that inflammation and OxS are associated with the incidence of MetS [9, 10]. Increased levels of C-reactive protein (representative of inflammation) and thiobarbituric acid reactive substances (representative of oxidative stress), along with a decrease in catalase activity, have been observed in postmenopausal women with MetS. It has also been reported that MDA is an independent predictor of MetS in middle-aged and elderly populations [9, 10]. In MetS, hyperglycemia and hyperlipidemia can increase ROS production, thereby inducing inflammation, leading to endothelial dysfunction, and resulting in increased endothelin-1 (ET-1) levels and decreased nitric oxide (NO) synthesis [4, 11]. ET-1 is an endogenous vasoconstrictor peptide produced by the vascular endothelium [12], associated with vascular inflammation, and implicated in various pathological conditions, such as hypertension, diabetes mellitus, and cardiovascular disease. Increased levels of ET-1 have been observed in patients with hyperglycemia, hypertension, diabetes mellitus, and MetS [12–15].

Melatonin (N-acetyl-5-methoxytryptamine), an endogenous hormone primarily produced by the pineal gland [16], plays a role in regulating circadian rhythm, mood, emotion regulation, immune function, and endocrine functions [17]. Studies suggest that melatonin supplementation may improve MetS components, including hyperglycemia, hypertension, dyslipidemia, and obesity [2, 18–20]. Melatonin is a potent antioxidant with radical-scavenging activity [20, 21], and its supplementation has been shown to improve OxS parameters. For instance, a 2020 study by Zare Javid et al. reported that melatonin supplementation significantly reduced serum MDA levels in type 2 diabetes mellitus patients undergoing non-surgical periodontal therapy [22]. Raygan et al. found that melatonin supplementation reduced MDA and increased plasma glutathione in diabetic patients with coronary heart disease, compared to a control group [23]. Another study by Szewczyk-Golec et al. demonstrated that melatonin supplementation attenuated OxS in obese patients on a calorie-restricted diet [24]. In addition to its antioxidant properties, melatonin exhibits anti-inflammatory activity and improves endothelial function [25]. An animal study reported that melatonin inhibited the increase in ET-1 gene expression following hepatic ischemia/reperfusion in rats and significantly decreased MDA concentration post-reperfusion [26].

Given that MetS involves a cluster of risk factors, identifying factors that can effectively treat and prevent MetS progression is crucial. Considering the role of OxS and inflammation in MetS pathogenesis and the known antioxidant and anti-inflammatory properties of melatonin, this study aims to examine the effect of melatonin supplementation on serum MDA and SOD activity levels, as well as ET-1 levels, in patients with MetS.

Materials and methods

The study was approved by the independent ethics committee of Ahvaz Jundishapur University of Medical Sciences, under Mrs. Bahrami's project (IR.AJUMS.REC.1395.702). It was also registered in the Iranian Registry of Clinical Trials (IRCT2016111016123N11).

The study population consisted of adult women and men with MetS, referred to the Golestan Hospital, Ahvaz Jundishapur University of Medical Sciences. This was a randomized, double-blind, placebo-controlled clinical trial with two identical treatment groups. The National Cholesterol Education Program (NCEP) criteria were used to define MetS. Subjects with 3 or more of the following criteria were defined as having MetS: waist circumference (WC) of >102 cm for men and >88 cm for women, fasting blood sugar (FBS) of ≥ 100 mg/dL, high-density lipoprotein cholesterol (HDL-C) level of <40 mg/dL for men and <50 mg/dL for women, triglyceride (TG) level of ≥ 150 mg/dL and systolic blood pressure (SBP) ≥ 130 mmHg and/or diastolic blood pressure (DBP) ≥ 85 mmHg.

Participants were categorized by sex and body mass index (BMI). The block randomization method was used to divide individuals into two groups (melatonin and placebo). A total of 63 patients were registered in the study, with 32 in the placebo group and 31 in the melatonin group. Before the study, patients' medical history, medication, family history, and demographics were collected. Simple random sampling, without an alternate method, was used to collect samples.

Patients with psychological instability, hypo- and hyperthyroidism, coronary heart disease, renal failure, gastrointestinal diseases, rheumatoid arthritis, a history of hypothyroidism, Cushing's syndrome, or those who underwent weight loss surgery in the last year were excluded. Lactating or pregnant women were also not included.

Anthropometric measurements

Participants' height and weight were measured after an overnight fast using a standard scale. BMI was then calculated,

and waist and pelvic measurements were taken. These measurements were repeated at the end of the intervention period. Patients' diets were evaluated at the beginning and end of the study through face-to-face and telephone interviews. Three validated questionnaires on physical activity, sleep, and appetite were completed.

Patients received supplements for 12 weeks as per their group assignment. The melatonin supplement group received a 6 mg/day melatonin capsule before bedtime, while the placebo group received a visually similar, starch-containing placebo capsule. Fasting blood samples (12 ml) were collected at baseline and after 12 weeks of intervention. Serum samples were stored at -70 °C until the end of sampling, after which the studied markers were measured using spectrophotometry and ELISA, according to kit instructions.

Sample size calculation

The computation of the sample size was influenced by Mesri Alamdari et al.'s research [27]. This study revealed that in the melatonin group, the mean and standard deviation of MDA before and after treatment amounted to 3.81 ± 0.29 and 2.79 ± 0.29, respectively, reflecting a difference of 1.02. In contrast, in the placebo group, the mean and standard deviation of MDA before and after treatment were 3.62 ± 0.28 and 2.96 ± 0.37, respectively, also yielding a difference of 0.66. To compare means between two independent groups, the following formula was utilized. This calculation resulted in a sample size of 30 subjects per group, taking into account a significance level of 0.05 and a power of 95%. Given the projected dropout rate of approximately 25% during the clinical trial, it is proposed to recruit 40 subjects for each group.

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \left(s_1^2 + s_2^2\right)}{\left(\mathrm{X}_1 - \mathrm{X}_2\right)^2}$$

Statistical analysis

All data were analyzed using IBM SPSS version 16.0 and GraphPad Prism version 5 software. Outcome measures are presented as the mean ± SEM. Data normality was checked with the Kolmogorov–Smirnov test, confirming a normal distribution for all data. An independent sample t-test was used to compare data between the two groups (melatonin and placebo), while a paired t-test was applied to assess pre- and post-intervention results within each group. An analysis of covariance (ANCOVA) was also performed to assess the effect of the intervention after adjusting for the baseline value. A p-value of less than 0.05 was considered statistically significant.

Results

We screened 110 participants, out of whom 30 eligible subjects chose not to continue participation. Consequently, 80 participants were included in the clinical trial (n = 40 in the placebo group and n = 40 in the melatonin group). Of these, 8 participants from the placebo group and 9 from the melatonin group dropped out due to personal reasons. Therefore, the study included 32 participants in the placebo group and 31 in the melatonin group. Figure 1 shows the details of the follow-up data. Tables 1 and 2 present the demographic data and the comparison of anthropometric measurements between the two study groups, respectively.

Table 3 presents the comparison of biomarkers of OxS (serum levels of MDA and SOD activity) and the serum level of ET-1 between the two study groups. No significant differences were observed in the serum level of ET-1 between the two study groups at baseline and post-intervention ($p \geq 0.05$). After 12 weeks of supplementation with melatonin, the melatonin group showed a significant reduction in ET-1 concentration compared with baseline (1.55 ± 0.24 pg/ml vs. 0.80 ± 0.18 pg/ml; $p = 0.040$). However, the decrease in serum level of ET-1 was not significant in the placebo group compared with baseline (1.15 ± 0.29 pg/ml vs. 0.92 ± 0.21 pg/ml; $p = 0.73$). Additionally, melatonin supplementation significantly reduced serum MDA in the melatonin group compared with baseline (1.32 ± 0.05 µM vs. 1.13 ± 0.05 µM; $p = 0.021$). In contrast, this parameter did not change significantly in the placebo group (1.27 ± 0.05 µM vs. 1.31 ± 0.05 µM; $p = 0.64$). At baseline, there were no significant changes in the serum level of MDA between the two study groups, but a significant difference was found post-intervention.

The comparison of serum SOD activity values in the melatonin and placebo groups before and after the intervention showed a significant increase in SOD activity in the melatonin group (23.64 ± 2.77 U/ml vs. 41.35 ± 1.22 U/ml; $p = 0.0001$) but not in the placebo group (28.85 ± 2.46 U/ml vs. 34.75 ± 1.190 U/ml; $p = 0.06$). Also, while there were no significant differences in SOD activity between the two study groups at baseline ($p \geq 0.05$), the difference post-intervention was significant.

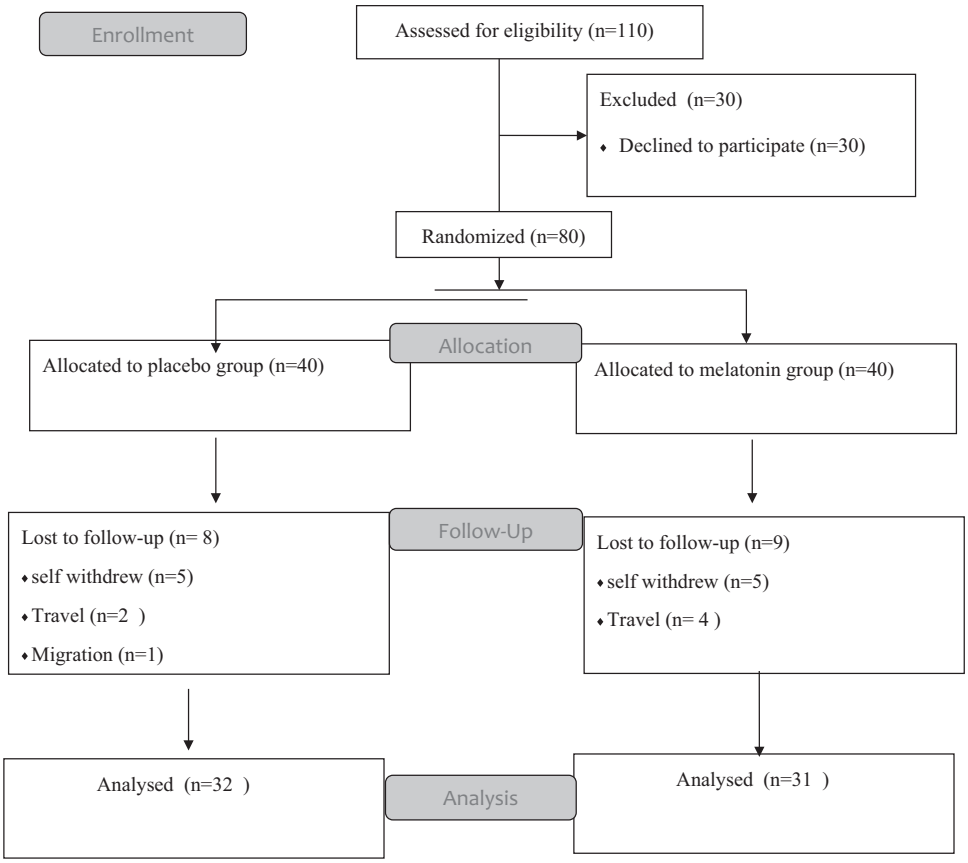

Fig. 1 Flowchart of participants' recruitment and follow-up

Table 1 Demographic data of study participants

Characteristics		Melatonin n = 31	Placebo n = 32	*p* value[#]
Gender (%)	Male	71.0%	59.4%	0.335
	female	29.0%	40.6%	
Education	≥ Diploma	45.1%	43.8%	0.178
	Associate's degree to Bachelor	22.6%	40.6%	
	< Bachelor	32.3%	15.6%	
Ethnicity	Bakhtiari	25.8%	18.8%	0.412
	Arab	29.1%	15.6%	
	Fars	41.9%	59.4%	
	Others	3.2%	6.2%	
History disease	Diabetes,Cardiovascular,renal disease	16.1%	15.6%	0.539
	Digestive disorders	25.8%	12.5%	
	Others	32.3%	34.4%	
	None	25.8%	37.5%	

[#]*p* value < 0.05 considered as significant

Discussion

This clinical trial investigated the impact of melatonin supplementation on OxS parameters and serum ET-1 levels in patients with MetS. Our study results demonstrated that 12 weeks of melatonin supplementation (6 mg/day) significantly decreased serum ET-1 and MDA levels and significantly increased SOD activity in patients with MetS.

OxS plays a significant role in the pathogenesis of MetS [4]. Melatonin, a hormone with antioxidant effects, can scavenge free radicals and ROS [28]. Numerous studies

Table 2 Anthropometric measures in melatonin and placebo groups

Parameters	Time	Group	N	Mean ± SD	*p* value[#]
Weight (Kg)	Baseline	melatonin	31	89.08 ± 14.42	0.531
		Placebo	32	91.48 ± 15.80	
	Week 12	melatonin	31	87.70 ± 14.84	0.376
		Placebo	32	91.32 ± 17.22	
Height (cm)		melatonin	31	171.64 ± 9.66	0.312
		Placebo	32	169.03 ± 10.64	
BMI	Baseline	melatonin	31	30.22 ± 4.04	0.119
		Placebo	32	32.05 ± 5.07	
	Week 12	melatonin	31	29.73 ± 4.10	0.066
		Placebo	32	31.95 ± 5.21	
WC (cm)	Baseline	melatonin	31	106.48 ± 7.61	0.493
		Placebo	32	108.12 ± 10.91	
	Week 12	melatonin	31	104.90 ± 7.82	0.202
		Placebo	32	108.06 ± 11.23	
HC (cm)	Baseline	melatonin	31	110.93 ± 6.63	0.120
		Placebo	32	114.28 ± 9.84	
	Week 12	melatonin	31	110.46 ± 6.27	0.130
		Placebo	32	113.78 ± 10.31	
Body fat percentage	Baseline	melatonin	31	0.32 ± 0.06	0.047
		Placebo	32	0.36 ± 0.06	
	Week 12	melatonin	31	0.32 ± 0.06	0.999
		Placebo	32	0.35 ± 0.06	

BMI body mass index, *WC* waist circumference, *HC* hip circumference

[#]*p* value < 0.05 considered as significant

Table 3 Comparison of serum markers between melatonin and placebo groups

parameters	Melatonin mean ± SEM	Placebo Mean ± SEM	*p*-value
ET-1 (pg/ml)			
Before	1.550 ± 0.2472	1.159 ± 0.2933	0.313[†]
After	0.808 ± 0.181	0.925 ± 0.213	0.682[‡]
p-value*	0.04	0.73	
SOD (U/ml)			
Before	23.64 ± 2.777	28.85 ± 2.467	0.169[†]
After	41.35 ± 1.222	34.75 ± 1.190	0.001[‡]
p-value*	0.0001	0.06	
MDA (μM)			
Before	1.326 ± 0.05611	1.276 ± 0.05829	0.542[†]
After	1.134 ± 0.053	1.314 ± 0.053	0.022[‡]
p-value*	0.021	0.64	

SOD superoxide dismutase, *MDA*malondialdehyde, *ET-1* Endothelin-1

* Values were obtained from paired-sample t test;

[†] Values were obtained from independent-samples t-test;

[‡] Values were obtained from ANCOVA test after adjusting for baseline values

$p < 0.05$ as significant difference

report reduced melatonin circulating levels in patients with coronary heart disease, hypertension, diabetes, and obesity [28]. There is accumulating evidence that melatonin supplementation may improve MetS components such as dyslipidemia, hypertension, hyperglycemia, obesity, and insulin resistance [18–20, 29]. In 2014, Goyal et al. found that melatonin intake (8 mg/day for 10 weeks) improved most MetS components in patients with MetS [30]. Melatonin's antioxidant properties have been shown to be effective in improving MetS, exerting its effects via mechanisms like free radical scavenging and stimulation of endogenous antioxidative enzymes [31]. Most studies have evaluated melatonin's role in multiple MetS components such as hypertension, HDL-C, and lipid profile [32]. In this study, we explored the impact of 12 weeks of melatonin administration on biomarkers of OxS (serum levels of MDA and SOD activity) and ET-1 levels in patients with MetS. Our findings showed that 12 weeks of melatonin administration significantly decreased MDA in patients with MetS, aligning with the study by Koziróg et al., who found that melatonin intake (5 mg/day for 8 weeks) decreased MDA levels in patients with MetS [20]. Numerous studies have reported that melatonin supplementation can improve MDA levels in patients with diabetes mellitus [22, 23, 33]. For instance, Raygan et al. noted a significant decrease in MDA levels in diabetic patients with coronary heart disease after taking 10 mg/day of melatonin for 12 weeks in comparison to the placebo group [23]. Kedziora-Kornatowska et al. observed a significant reduction in MDA levels and an increase in SOD-1 activity in type 2 diabetic patients after consuming 5 mg/day of melatonin for 30 days [34]. Furthermore, a clinical trial revealed that 12-week melatonin supplementation (2 × 5 mg/day) significantly reduced plasma MDA and increased plasma total antioxidant capacity in diabetic hemodialysis patients [35]. Various mechanisms have been proposed to explain the effects of melatonin on decreasing MDA, including the detoxification of free radicals and reactive oxygen intermediates, which are responsible for the increase in MDA production via lipid peroxidation [36].

Patients with MetS have been reported to have lower antioxidant enzyme activities and higher levels of OxS markers [4]. Previous clinical trials have suggested that melatonin intake can significantly increase the activity of enzymatic antioxidants such as SOD and GPx [22]. These enzymatic antioxidants can defend against free radicals and nascent oxygen [37]. In our study, we observed an increase in SOD activity in patients who consumed melatonin supplements for 12 weeks compared to control subjects. A study by Zare Javid et al. supports our findings; they reported a significant increase in SOD activity in type 2 diabetes mellitus patients with periodontal disease after melatonin supplementation of 250 mg/day for 8 weeks [22].

High serum ET-1 is associated with the components of MetS, including hypertension, hyperglycemia, and obesity [38]. While several studies have shown that melatonin can decrease circulating ET-1 [39–41], data is insufficient regarding the influence of melatonin supplementation on circulating ET-1 in patients with MetS. In our study, we found that 12-week melatonin administration significantly decreased serum ET-1 in patients with MetS.

Our study, along with others [36, 42, 43], suggests that melatonin consumption can protect against ROS and stimulate antioxidant enzymes activity. Accumulating evidence confirms that OxS plays an important role in the pathogenesis of MetS [4]. Melatonin, a potent free radical scavenger, has demonstrated the ability to scavenge ROS and free radicals [28], suggesting that it could serve as a potential therapeutic agent for MetS.

This study has several limitations. Firstly, due to the small sample size, we could not conduct a stratified analysis based on gender. Secondly, we did not measure the serum concentration of melatonin, which could have helped assess patient compliance with the drug. Lastly, due to budget limitations, we were unable to measure other biomarkers of OxS (such as glutathione peroxidase and glutathione reductase) and inflammation (IL-6 and TNF-α).

Conclusion

Our findings demonstrated that 12 weeks of melatonin supplementation in patients with MetS significantly decreased serum ET-1 and MDA levels and increased SOD activity. These results strongly support the potential of melatonin as an antioxidant component for use in preventing MetS complications, such as cardiovascular disorders and diabetes mellitus. Melatonin has a safe profile with minimal side effects, which include dizziness and headaches [44]. Given these advantages, melatonin could be recommended as an adjunct to MetS treatment. Further studies with larger sample sizes and different doses in various populations are needed to evaluate melatonin's efficacy in treating MetS.

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Data Acquisition:SJ, ZN.
Data Analysis: SA.
Drafting the Manuscript: HG-Z, MHR, FS, RN-M.
Critical Revising of the Manuscript: HB-R, HG-Z.
Final Approval of the Manuscript: HB-R.

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Data availability Upon request we can provide the data.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical clearance Subjects aged 18 and above who met the criteria of the National Diabetes Association for the diagnosis of metabolic syndrome were eligible to participate. Informed written consent was obtained from all study subjects.

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ORIGINAL ARTICLE

The association of HbA1C and cTnI with mortality and severity of disease among patients with acute coronary syndrome

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Abstract

Objective In the present study, we aimed to evaluate the association of glycosylated hemoglobin A1c (HbA_1C) and cardiac troponin I levels (cTn1) with the 30-day mortality and severity of myocardial infarction in patients presenting with ACS.

Methods The present cross-sectional study was done over two years in the medical centers of Zabol University of Medical Sciences. All patients who were referred to the cardiovascular emergency department between 2017 and 2019 presenting with acute coronary syndrome were included. Serum cTn1 and HbA_1C concentration were measured between 12 and 48 h after the onset of chest pain, and the mortality rate of these patients was studied by the census method. All statistical analysis was done using SPSS software.

Results There was a significant difference in the cTn1 level between patients with SYNTAX scores higher than 22 and the rest of patients (96 ± 11.3 versus 71 ± 17.8). The patients who were diagnosed with acute MI showed significantly higher levels of HbA_1C compared to unstable angina cases (6.9 ± 1.2 versus 5.2 ± 0.8). The results of pearson correlation showed a positive correlation between HbA_1C levels and cTn1 levels (correlation coefficient: 0.80, $p < 0.001$) (Fig. 1). In addition, there was a positive correlation between HbA_1C and SYNTAX score (correlation coefficient: 0.45, $p < 0.001$). The HbA_1C level was significantly higher among the deceasesd patients compared to the survived cases (7.8 ± 0.7 versus 6.0 ± 1.3).

Conclusion In conclusion, our study underscores the prognostic importance of HbA1C and cTnI, especially in the STEMI subset within the larger ACS cohort. The association of these markers with a heightened 30-day mortality rate in STEMI patients stands out. Yet, it is paramount to emphasize that these observations are predominantly tailored to the STEMI subset and may not universally apply to all ACS patients. The null mortality in our NSTEMI cohort punctuates the need for more refined research to discern the implications of HbA1C and cTnI across diverse ACS subgroups.

Keywords Troponin · HbA_1C · 30-day mortality · Cardiovascular disease

Introduction

Cardiovascular disorders are globally recognized as a leading cause of mortality and morbidity [1]. This scenario is similarly replicated in Iran, where, according to the World Health Organization, cardiovascular diseases constitute the majority of non-communicable disease-related deaths [2]. Every year, a substantial number of these deaths are attributed to new or recurring myocardial infarction (MI) events [2], alongside the numerous silent MIs that often remain undiagnosed [1]. This persistent and unmitigated incidence of MIs underscores the critical implications of this condition in the Iranian population (Tables 1, 2 and 3).

The diagnosis of acute myocardial infarction (AMI) is typically dependent on the detection of cardiac troponin I (cTnI) [3]. Based on the Third Universal Definition of Myocardial Infarction [3], the diagnosis of AMI necessitates a rise and/or fall of cTnI values, with at least one measurement exceeding the 99th percentile, in conjunction with clinical evidence of ischemia [1, 3]. While cTnI levels are frequently measured during emergency assessments of patients with ST segment elevation myocardial infarction (STEMI) [4–6], these measurements are not part of the formal diagnostic criteria. Previous studies have indicated that the kinetics of cTnI can provide valuable insights into the onset time of myocardial infarction, as well as establish significant

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Table 1 The general characteristics of the included ACS patients

Charcteristic	Value
Male sex, *n* (%)	149 (60.8%)
Age (mean ± SD) years	64.2 ± 11.1
Age > 50 years, *n* (%)	153 (62.4%)
BMI > 25, *n* (%)	103 (42%)
Hypertension, *n* (%)	137 (56%)
Dyslipidemia, *n* (%)	35 (14.2%)
Smoking, *n* (%)	81 (33%)
Diabetes, *n* (%)	124 (50.6%)
Familial history of CAD, *n* (%)	62 (25.3%)

Table 2 The clinical characteristics of the included ACS patients

Charcteristic		Value
Unstable angina		87 (35.5%)
NSTEMI		114 (46.5%)
STEMI		44 (18%)
SYNTAX score, median (IQR)		16 (9–24)
SYNTAX score > 22, *n* (%)		67 (27.3%)
Obstructive CAD		180 (73.4%)
Number of involved vessels	None	5 (2%)
	Single	98 (40%)
	Two	74 (30.2%)
	Three	68 (27.7%)
Management	PCI	173 (70.6%)
	CABG	72 (29.4%)

correlations with the size of myocardial infarction and long-term mortality [7].

Additionally, heightened levels of glycosylated hemoglobin A1c (HbA1C), an established marker for long-term glycemic control, have been linked with an increased risk of cardiovascular diseases in diabetic patients [8], and even all-cause mortality [9]. It is well-established that elevated HbA1C levels can result in unfavorable outcomes for patients suffering from myocardial infarction [10]. Nevertheless, there is a scarcity of data concerning the correlation between HbA1C levels and the severity of myocardial infarction. In this study, we aimed to evaluate the association of HbA1C and cTnI levels with 30-day mortality and the severity of myocardial infarction among patients presenting with Acute Coronary Syndrome (ACS) in Iran.

Materials and methods

Study design

This research was an observational cross-sectional study conducted over two years at medical centers affiliated with Zabol University of Medical Sciences.

Study population

From January 2017 to 1st January 2019, we evaluated all patients referred to the cardiovascular emergency department of Zabol University of Medical Sciences with a presenting

Table 3 The relation between troponin and HbA_1C levels and different variables

Variable		Troponin (ng/l)	*p* Value	HbA_1C level (%)	*p* Value
Death/live	Death	171.6 ± 34.2	$p < 0.001$	7.8 ± 0.7	$p < 0.001$
	Live	75.5 ± 70.3		6.0 ± 1.3	
Acute MI	+	136.35 ± 54.3	$p < 0.001$	6.9 ± 1.2	$p < 0.001$
	-	11.3 ± 5.3		5.2 ± 0.8	
MI	STE	140.21 ± 24	0.14	6.8 ± 0.9	0.42
	NSTE	134.12 ± 38		6.5 ± 1.2	
Diabetes	+	150.5 ± 57.2	0.04	7.9 ± 2.1	$p < 0.0001$
	-	41 ± 44.6		5.2 ± 0.5	
Hypertension	+	128.9 ± 63.3	0.07	6.9 ± 1.3	0.06
	-	71.6 ± 52.5		5.5 ± 1.1	
Dyslipidemia	+	134.8 ± 65.4	0.09	07 ± 1.3	0.56
	-	77.9 ± 72.7		6.1 ± 1.4	
Smoking	+	101.8 ± 78.1	0.06	6.6 ± 1.4	0.11
	-	83.6 ± 72.2		6.1 ± 1.3	
BMI > 25	Yes	68.2 ± 45.7	0.88	6.6 ± 0.8	0.04
	No	67.4 ± 37.2		5.7 ± 0.4	
SYNTAX score > 22	Yes	96 ± 11.3	0.003	7.7 ± 1.1	0.02
	No	71 ± 17.8		5.6 ± 1.5	

complaint of acute coronary syndrome (ACS). For patients referred multiple times within the study timeframe, only the first referral was considered for analysis.

Inclusion criteria

1. Patients presenting with symptoms of ACS as defined by the AHA guideline, which includes cases of ST-elevation MI, non-ST elevation MI, and unstable angina [11].
2. Patients who underwent coronary angiography. This criterion was vital as the SYNTAX score, an angiography-based tool, was used to determine the severity of their coronary artery disease (CAD).

Exclusion criteria

Patients with incomplete angiography data as well as the patients who previously had a major cardiovascular intervention (PCI or CABG) were excluded. Patients having underlying conditions which affect HbA_1C such as chronic kidney disease and/or anemia were also excluded.

Study metrics and diagnosis

The severity of CAD in the patients was classified using the SYNTAX score. A SYNTAX score higher than 22 was deemed indicative of severe CAD [12, 13]. All diagnoses were coded using the 10th version of the International Classification of Diseases, Clinical Modification (ICD-10-CM). American College of Cardiology/American Heart Association [ACC/AHA] guideline was used for dyslipidemia diagnosis [14].

For patients diagnosed with ST-elevation myocardial infarction (STEMI), the primary mode of treatment was either thrombolysis or primary percutaneous coronary intervention (PCI). The choice between these two interventions was based on the clinical presentation, time since symptom onset, and the facility's capabilities.

We collected the venous blood samples from all patients for fasting blood glucose and HbA1c, and lipid profile after an overnight 8-h fasting. All patients were evaluated by electrocardiogram and cardiac enzymes, after being examined regarding vital signs and blood pressure.

HbA1c was measured using the high-performance liquid chromatography (HPLC) method, while cTn1 concentration was measured using the enzyme-linked immunosorbent assay (ELISA) method. Serum cTn1 concentration was measured between 12 and 48 h after the onset of chest pain, and the mortality rate of these patients was studied by the census method.

The cTn1 I level of ≥ 0.1 ng/ml was considered positive, and a cTn1 level lower than 0.1 ng/ml was considered negative.

Thirty-day mortality was compared between patients with positive and negative cTn1 based on cTn1 level. The patients were informed of the data collection, and it was guaranteed that the information was kept safe and the study was approved by the University Ethics Committee.

Data analysis

We expressed the continuous and normally-distributed variables as mean $\pm$ standard deviation(SD) and the non-normally distributed ones as median and interquartile (IQR).

Student *t*-test was used for analyzing continuous data, chisqure test for categorical data, and the Mann Whitney *U* test was used to analyze non-normaly distributed data. We used linear regression in order to evaluate the association between cTn1 and mortality, as well as HbA_1C and mortality. We also used logistic regression for assessing the association between SYNTAX > 22 and cTn1 levels and SYNTAX > 22 and HbA_1C levels.

The Pearson correlation coefficient was used to analyze and describe the data. All statistical analysis was done using SPSS (24^{th} version) software.

Descriptive statistics

In this study, 292 patients were screened, with 245 meeting the inclusion criteria. The composition of this cohort comprised 61% men and 39% women. The participants had an average age of 64.2 ± 11.1 years, with a majority of 153 (62.4%), being older than 50 years. Delving into their medical histories, 137 (56%) of these patients had a history of hypertension, 124 (50.6%) had diabetes mellitus, 35 (14.2%) reported dyslipidemia, 81 (33%) were smokers, and 62 (25.3%) had a family history of premature CAD.

Main clinical outcomes

Out of the 245 patients, 158 (64.4%) presented with a cTn1 level ≥ 40 ng/l. This subset included 114 (46.5%) with non-ST elevation MI and 44 (18%) with ST elevation MI. In terms of treatment, 173 patients underwent percutaneous coronary intervention (PCI), while 72 needed coronary artery bypass graft (CABG). Unfortunately, 17 (6.9%) of the patients died within 30 days of admission, all of whom were in the MI groups.

Biomarkers and associated clinical findings

The average cTn1 level among the myocardial infarction patients stood at 136.35 ± 54.3 ng/l. It was observed that deceased patients had a considerably higher mean cTn1 level of 171.6 ± 34.2 ng/l, contrasting with the survivors whose

mean was 75.5 ± 70.3 ng/l ($p < 0.0001$). Furthermore, a notable difference in cTn1 levels was discerned between those with SYNTAX scores exceeding 22 and their counterparts, averaging at 96 ± 11.3 versus 71 ± 17.8 ng/l, respectively. Particularly, patients diagnosed with diabetes exhibited significantly elevated mean cTn1 levels, amounting to 150.5 ± 57.2 ng/l, in contrast to 41 ± 44.6 ng/l in non-diabetic patients ($p < 0.05$). However, there were no discernible differences in troponin and HbA1C levels when comparing ST-elevated and non-ST-elevated MI patients. Furthermore, cTn1 levels did not significantly vary based on smoking habits or BMI.

Shifting focus to HbA1C levels, it was evident that deceased patients had markedly elevated levels at 7.8 ± 0.7 compared to survivors, who averaged 6.0 ± 1.3. Moreover, acute MI diagnosed patients exhibited HbA1C levels of 6.9% ± 1.2, which was higher than those with unstable angina at 5.2% ± 0.8. When categorized based on the SYNTAX score, patients scoring over 22 displayed elevated HbA1C levels of 7.7% ± 1.1 against 5.6% ± 1.5 in others. Additionally, those with a BMI exceeding 25 were found to have significantly higher HbA1C levels.

Correlations and advanced statistical analysis

The Pearson correlation indicated a strong positive relationship between HbA1C and cTn1 levels, with a correlation coefficient of 0.80 ($p < 0.001$) as depicted in Fig. 1. There was also a positive association between HbA1C levels and SYNTAX scores, with a correlation coefficient of 0.45 ($p < 0.001$). Regression analysis insights revealed an independent association between HbA1C levels and both SYNTAX score and mortality (β values being 0.09 and 0.07, respectively, with p values < 0.05). cTn1 also exhibited independent correlations with SYNTAX and mortality, with β values of 0.20 and 0.36, respectively, and p values < 0.05. The combined influence of HbA1C and cTn1 on SYNTAX and mortality was measured at 0.11 and 0.29, respectively.

Discussion

In our investigation into the prognostic utility of troponin and HbA1C for patients with ACS admitted to the emergency department, we unearthed some compelling findings. Our data indicating elevated mortality rates among patients with heightened troponin and HbA1C levels echoes the overarching trends evidenced in the wider body of literature.

The diagnostic and prognostic prominence of cardiac troponin, especially cTnI, in the realm of myocardial infarction (MI) is well-documented [15, 16]. cTnI's specificity to myocardial damage means that its elevated levels typically signify myocardial injury. Crucially, the magnitude of this elevation often correlates with the severity of the myocardial damage, which can, in turn, be a harbinger of patient outcomes [17]. This relationship between cTnI and myocardial damage has been validated by multiple studies, underscoring these prognostic implications. Studies by Boeddinghaus [18] and Than et al. [19], for instance, solidify our observations by emphasizing the link between raised cTn levels

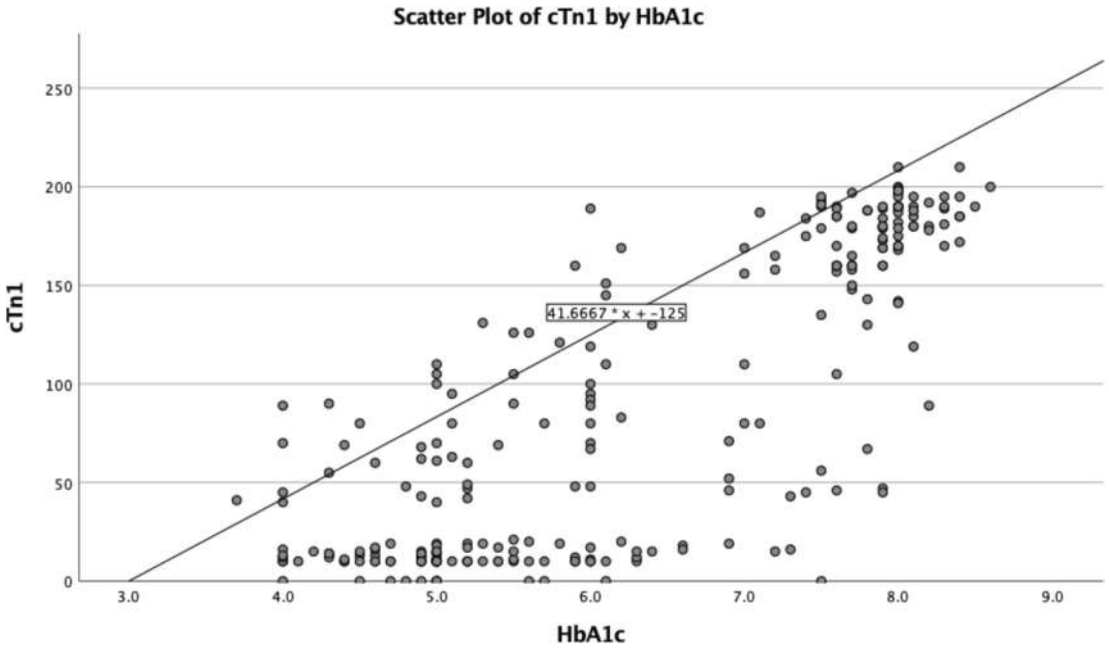

Fig. 1 Scatter plot of correlation between cTn1 and HbA_1C

and an augmented risk of major adverse cardiac events and mortality.

Diabetes mellitus (DM) has historically been considered a predictor of mortality in ACS patients [20]. However, previous data suggests that HbA1C might hold predictive value even in the absence of a diabetes diagnosis. Supporting this, findings by Kilic et al. [21] discerned a strong correlation between HbA1C levels and the severity of MI in nondiabetic NSTEMI patients. This perspective invites the consideration that assessing HbA1C levels may be of clinical import even for those without a pre-existing diagnosis of diabetes, offering a potential avenue for improved risk stratification in ACS patients.

Further, we noted a positive relationship between cTn1 and HbA1C levels in our cohort, a trend also seen in the study by Kilic et al. [21]. This association suggests that HbA1C might be linked to conditions that lead to a spike in cTn1 levels, such as stroke, arrhythmia, and pulmonary emboli. While recent literature has hinted at this relationship, the intricate mechanics of this linkage remain clouded, indicating a potential avenue for subsequent research [22].

Another salient finding was the heightened HbA1C and cTn1 levels observed among ACS patients presenting with a SYNTAX score exceeding 22. Given the SYNTAX score's repute as a tool to gauge the severity of coronary artery disease [23], it is feasible to suggest a correlation between MI severity and HbA1C levels. This observation was consistent across our STEMI and NSTEMI subgroups, hinting at the possibility that the severity of coronary disease might be intrinsically tied to these markers.

Conclusion

In conclusion, our study underscores the prognostic importance of HbA1C and cTnI, especially in the STEMI subset within the larger ACS cohort. The association of these markers with a heightened 30-day mortality rate in STEMI patients stands out. Yet, it is paramount to emphasize that these observations are predominantly tailored to the STEMI subset and may not universally apply to all ACS patients. The null mortality in our NSTEMI cohort punctuates the need for more refined research to discern the implications of HbA1C and cTnI across diverse ACS subgroups.

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Data Availability Please contact author for data requests.

Declarations

Ethics approval The study conforms to the Declaration of Helsinki and was approved by the ethical committee of Zabol University of Medical Sciences.

Consent to participate All patients provided their verbal consent as well as filling a written consent form.

Consent for publication Not applicable.

Competing interests Neither of the authors has any conflict of interest to disclose.

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VISION STATEMENT

To be recognized as a global leader for clinical care, education, training, research, advocacy and capacity building in the field of diabetes.

MISSION STATEMENT

1. Promotion of excellence in diabetes care to make India the Diabetes Care Capital
2. Empowerment of persons living with diabetes
3. Support for diabetes research
4. Dissemination of information and knowledge in diabetes care
5. Advocacy for the cause of diabetology

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Research proposal should have following proofs-

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2. A detailed budget
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20% of the grant amount will be disbursed initially. 30% of payment after receiving your project status report and utilisation of sanctioned amount, 25% on further completion and pending 25% on final submission of your project. All reports must be uploaded on the RSSDI Online Research Grant Platform.

Responsibility:
All grant awardees are expected to present their work at RSSDI Annual Conference during research presentation's session. Failure to file progress reports annually and when requested by the RSSDI and failure to present progress at RSSDI Annual conference may result in the forfeiture of the grant.

All awardees are expected to follow the tenets of responsible and ethical conduct of research. Unethical or fraudulent use of RSSDI research funds will warrant adverse action from the society including forfeiture of grant, black listing in the society's databases and other legal recourses that are available to the society.

Publication
The RSSDI expects that the grant source be acknowledged in all publications and submissions made with regards to the research done with the grant.

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Research proposals are invited from Indian scientists, who are members of RSSDI interested in conducting research in the field of Diabetes, Endocrinology& Metabolism, for funding by RSSDI

The proposals may of clinical or translational research importance. A maximum grant amount of INR 5 Lakhs will be sanctioned. All grants will be reviewed by the research committee.

The detailed proposals should include the following:
Title, names of principal and co investigators, summary, introduction/ background, review of literature, aims, methodology, study design and detailed plan of work & bibliography.

Brief biodata of principal investigator and other co-investigators.

Importance of work
Detailed Budget sought along with full justification/ proposed utilization, of funding sought from RSSDI

Whether the project is being partly funded from any other source? If yes, please mention the source and the amount received.

Ethics Committee clearance of the Institution or other bonafide body.

How to apply
Upload your Research proposals on the RSSDI Online Research Grant Platform.

When to apply
Proposals will be accepted every quarter of a year. The first month will be for the proposal submission, the second month for the scrutiny of the submitted proposals and the third month for the grant disbursement. This cycle will repeat for each quarter.

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- Applicant should submit Oral paper / Poster acceptance document to RSSDI Secretariat.
- Applicant should submit Declaration that he/she has not receiving grant from any other agency / Organization – In case of receiving grant from any other Organization, RSSDI shall pay only the exceeding amount not covered by that agency.

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11.	Down Town Hospital	Guwahati, Assam
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21.	Sarvodaya Hospital and Research Centre	Faridabad, Uttar Pradesh