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ORIGINAL ARTICLE

Effect of dapagliflozin on the triglyceride-glucose index and the atherogenic index of plasma used as markers of atherosclerosis in patients with type 2 diabetes mellitus

Deniz Gezer[1,2] · **Semra Özkan Öztürk**[1] · **Zehra Kocaman**[1]

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Abstract

Objective Atherogenic index of plasma (AIP) and triglyceride-glucose (TyG) index are inexpensive and non-invasive markers with high predictive value for early detection of cardiovascular disease in DM patients. Herein, dapagliflozin reduced the AIP and TyG and caused positive cardiovascular effects in patients with type 2 diabetes mellitus (T2DM).

Methods We retrospectively evaluated the data of patients aged >18 years with T2DM ($n = 348$; 210 [60.3%] women and 138 [37.7%] men; mean age = 59.24, standard deviation [SD] = ±10.44 years) who presented to a single-center internal medicine outpatient clinic between June 01, 2017, and December 30, 2020, and who were started on dapagliflozin as part of their treatment. Demographic data and clinical data of the patients at 0, 6, 12, and 24 months were retrieved from the electronic medical records of the hospital.

Results Hypertension was the most common comorbidity ($n = 155$ [48.9%] patients). AIP values measured before dapagliflozin initiation (mean = 0.68; SD, 0.33) and at 6 months (mean = 0.62; SD, 0.30) were significantly different ($p < 0.00$). Furthermore, TyG index values measured before initiation of medication (mean = 9.98; SD, 0.76) and at 6 months (mean = 9.73; SD, 0.71) were significantly different ($p < 0.00$). These differences persisted until 12 and 24 months after treatment initiation.

Conclusions Dapagliflozin administration lowered the AIP and TyG index in patients with T2DM; this may slow the atherosclerotic process and prevent the associated macrovascular complications.

Keywords Type 2 diabetes mellitus · Dapagliflozin · AIP · TyG · Atherosclerosis

Introduction

Diabetes mellitus (DM) is a major public health problem with an increasing prevalence worldwide [1]. Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of increased morbidity and mortality in patients with diabetes. The risk of cardiovascular death (CVD) events is approximately twice as high in patients with type 2 diabetes mellitus (T2DM) compared with those without T2DM, which has made cardiovascular prevention an important goal in the treatment of T2DM [2, 3].

Dapagliflozin is a selective sodium-glucose co-transporter 2 inhibitor (SGLT2i) that induces glycosuria and lowers plasma glucose by preventing glucose reuptake via proximal renal tubules. Animal experiments have suggested that dapagliflozin exerts an antiatherogenic effect through SGLT2 inhibition which reduces intestinal cholesterol absorption, thereby increasing fecal excretion of LDL and macrophage-derived cholesterol, potentially reducing LDL retention in the arterial intima [4].

In cardiovascular safety studies, SGLT2 inhibitors reduced plasma glucose while reducing systolic blood pressure, diabetic kidney disease, and heart failure and facilitating weight loss [5, 6]. This drug reduces mortality in patients with chronic heart failure and reduced ejection fraction and in patients with chronic renal failure, regardless of the presence or absence of T2DM [7–9].

✉ Deniz Gezer
drdenizgezer@gmail.com

[1] Departman of İnternal Medicine, Mersin City Training and Research Hospital, Mersin, Turkey

[2] Mersin City Research and Education Hospital, Mersin, Turkey

Current guidelines strongly recommend SGLT2i therapy in patients with chronic heart failure and reduced ejection fraction [10]. The atherogenic index of plasma (AIP) and the triglyceride-glucose (TyG) index are markers with high predictive value for the early detection of cardiovascular disease in patients with DM [11, 12]. The TyG index is an independent risk factor for DM and the incidence of coronary atherosclerosis [13]. AIP was reported to be a reliable indicator for cardiovascular disease [14].

The purpose of the present study was to investigate whether dapagliflozin can serve as an acceptable treatment option in preventing the progression of atherosclerosis. To this end, we evaluated the long-term—at 0, 6, 12, and 24 months—effects of dapagliflozin on the AIP and the TyG index in T2DM patients who presented to Mersin Training and Research City Hospital Internal Medicine outpatient clinic between June 01, 2017, and December 30, 2020.

Methods

This study retrospectively assessed patients aged >18 years who presented to the internal medicine outpatient clinic of Mersin Training and Research City Hospital between June 01, 2017, and December 30, 2020, who were diagnosed with T2DM and were started on dapagliflozin as part of their treatment. Patients were included in the study if they had T2DM and were started on dapagliflozin; they were excluded if they had type 1 diabetes mellitus (T1DM) or did not attend follow-up checks. Patients' data related to age, sex, comorbidities, medications, time of diagnosis, and laboratory test results at 6, 12, and 24 months were retrospectively retrieved from electronic medical records.

Study data were processed using the SPSS 20·0 software suite. Data analysis was preceded by missing data analysis, as suggested by Bennet (2001); the missing data were distributed in the form of missing completely at random (MCAR) (Little's MCAR test: $p > 0.05$). Therefore, the missing data were completed through group averaging. Data were analyzed using descriptive and inferential statistics.

Before the analyses, data were checked for normality of distribution using Skewness–Kurtosis, histograms, and Kolmogorov–Smirno tests. Normally distributed data for continuous variables were reported in mean and standard deviation, whereas non-normally distributed data were reported in median and interquartile range. Categorical variables were presented using frequencies and percentages. AIP was calculated using the formula log10(TG/HDL-C) [13]. TyG index was calculated using the formula Ln[TG × FBG/2] [15]. Differences between time-dependent repeated measurements of AIP and TyG indices were determined using repeated measures ANOVA analysis. Intergroup differences of categorical variables were compared using the chi-square test or Fisher's exact test depending on the parametric data relating to the variables. Statistical significance was set at 0.05.

The study received approval from the Non-Invasive Clinical Research Ethics Committee of the Mersin University (2023/291).

Results

For the period between June 01, 2017, and December 30, 2020, there were 745 patients who had T2DM and who were started on dapagliflozin in addition to their existing therapies. Patients were excluded if they were pregnant or lactating, were started on hyperlipidemia medications during follow-up, consumed alcohol, and had incomplete follow-up data. Therefore, the analysis finally included 348 patients. Of the patients included in the study, 210 (60.3%) were women and 138 (37.7%) were men, with a mean age of 59.24 (standard deviation [SD], 10.44) years and average diabetes duration was 10.36 ± 5.32 years. The most common comorbidity was hypertension, seen in 155 (48.9%) patients. The patients were started on dapagliflozin in addition to the medications they had been prescribed for existing diseases. The demographic data of the patients are presented in Table 1.

Laboratory test results of the patients before initiation and at 6, 12, and 24 months after initiation of dapagliflozin are presented in Table 2.

Table 1 Demographic data of the patients

Feature	All patiens (*n*=348)
Gender	
Female, *n* (%)	210 (60.3)
Male, *n* (%)	138 (39.7)
Age, $\bar{x}$ (ss)	59.24 (10.44)
Additional drugs	
Calcium channel blocker, *n* (%)	38 (10.9)
Beta blocker, *n* (%)	42 (12.1)
Statin/fenofibrate, *n* (%)	107 (30.7)
Metformin, *n* (%)	229 (65.8)
Dpp-4 inhibitor, *n*(%)	134 (38.5)
Sulfonylurea, *n* (%)	50 (14.4)
Insulin users, *n* (%)	80 (23)
Thiazolidinedione, *n* (%)	55 (15.8)
Glinid, *n* (%)	8 (2.3)
ARB_ACE inhibitor, *n* (%)	115 (33)
Additional diseases	
Cancer, *n* (%)	4 (1.3)
Coronary artery disease, *n* (%)	30 (9.5)
Hyperlipidemia, *n* (%)	110 (34.7)
Hypertension, *n* (%)	155 (48.9)
Cerebrovascular ischemia, *n* (%)	1 (0.02)
Congestive heart failure, *n* (%)	4 (1.3)
Chronic obstructive pulmonary disease, *n* (%)	13 (4.1)

Table 2 Laboratory test results before and after initiation of medication

Laboratory test results	Before initiation of medication	After initiation of medication		
	1. Measurement	2. Measurement (6 months)	3. Measurement (1 year)	4. Measurement (2 years)
Fasting plasma glucose (mg/dL)	216 (113)[a]	180.50 (91.75)[a]	193.50 (79.8)[a]	179 (96)[a]
HBA1C (%)	9.2 (2.8)[a]	8.77 (1.50)[a]	8.75 (1.8)[a]	8.85 (1.9)[a]
Creatinine (mg/dL)	0.8 (0.3)[a]	0.8 (0.3)[a]	0.8 (0.2)[a]	0.8 (0.3)[a]
ALT (U/L)	21 (13)[a]	22 (10.75)[a]	21 (10)[a]	21 (10)[a]
AST (U/L)	18 (9.75)[a]	20 (8)[a]	21 (8)[a]	20 (9)[a]
Triglyceride (mg/dL)	199 (132.7)[a]	209 (95)[a]	209 (88.8)[a]	210.5 (110.8)[a]
LDL cholesterol (mg/dL)	111.61 (36.4)[b]	108.82 (32.75)[a]	105.07 (31)[b]	105.79 (32.79)[b]
HDL cholesterol (mg/dL)	43 (13)[a]	46 (11.34)[a]	46.28 (10)[a]	47 (12)[a]
Total cholesterol (mg/dL)	197.50 (53.5)[a]	95.46 (41)[a]	189.34 (33.8)[a]	195.94 (42.13)[b]
Na (mEq/L)	139 (3)[a]	139 (3)[a]	138.7 (2)[a]	139 (3.5)[a]
K (meq/L)	4.7 (0.5)[a]	4.7 (0.4)[a]	4.7 (0.8)[a]	4.63 (0.45)[b]
Mg (mg/dL)	1.96 (0.1)[a]	1.98 (0.01)[a]	1.95 (0)[a]	2.1 (0.1)[a]
Hematocrit (%)	41 (6.68)[a]	41.09 (6.18)[a]	40.99 (5.3)[a]	41 (5.9)[a]
Hemoglobin (g/dL)	13.65 (2.2)[a]	13.74 (2.28)[a]	13.61 (1.6)[b]	13.95 (2.3)[a]

[a]Non-normally distributed data in median and interquartile range in parentheses; [b]normally distributed data in mean and standard deviation in parentheses

The time-dependent effect of dapagliflozin on the AIP was evaluated using repeated measures ANOVA. The analysis detected a significant difference between at least two groups in terms of AIP. Furthermore, Mauchly's test of sphericity—one of the assumptions of the analysis—having yielded a significant result, the Greenhouse–Geisser value was reported, $F(3.1041) = 6.624$, $p = 0{\cdot}00$. Post hoc analysis with Bonferroni correction was used to determine which measurements led to significant differences. The results showed a significant difference between the first and second measurement and between the first and third measurement. Therefore, a significant difference ($p < 0.00$) was noted between the AIP values before initiation of dapagliflozin (at baseline) (mean, 0.68; SD, 0.33) and at the second measurement (mean, 0.62; SD, 0.30). Additionally, a significant difference was observed between the AIP values at baseline (mean, 0.68; SD, 0.33) and at the third measurement (mean, 0.63; SD, 0.26) ($p < 0.00$). Data on these findings are shown in Table 3.

The time-dependent effect of dapagliflozin on TyG was evaluated using repeated measures ANOVA test. The analysis revealed a significant difference between at least two groups in terms of TyG, $F(3.345) = 12.95$, $p = 0.00$. Post hoc analysis with Bonferroni correction was used to determine which measurements were responsible for the significant differences. The findings showed significant differences between the first measurement and the next three measurements. Thus, there was a significant difference ($p < 0.00$) between the TyG values at baseline (mean, 9.98; SD, 0.76) and at the second measurement (mean, 9.73; SD, 0.71). Additionally, a significant difference ($p < 0.00$) was observed between the TyG values at baseline and at the third measurement (mean, 9.78; SD, 0.65). Likewise, a significant difference ($p < 0.00$) was noted between the TyG values at baseline and at the fourth measurement (mean, 9.78; SD, 0.65). Data on these findings are given in Table 4.

Use of medication for hyperlipidemia

To determine the effect of hyperlipidemia medications (statin and fenofibrate) on the analysis results, the tests for the AIP and TyG were repeated among those who did not use medication and ANOVA findings showed that the significant relationship persisted at a level of 0.03.

Table 3 Time-dependent changes in AIP in patients receiving dapagliflozin

AIP value	Average	Standard deviation	*F*	*p*	Post hoc
1. Measurement, $\bar{x}$ (ss)	0.686	0.33	*F*=5.96	<0.00	1>2**
2. Measurement (6 months), $\bar{x}$ (ss)	0.622	0.30			1>3**
3. Measurement (1 year), $\bar{x}$ (ss)	0.629	0.26			
4. Measurement (2 years), $\bar{x}$ (ss)	0.643	0.31			

Table 4 Time-dependent changes in the triglyceride-glucose index

TyG value	Average	Standard deviation	*F*	*p*	Post hoc
1. Measurement, $\bar{x}$ (ss)	9.98	0.76	13.01	<0.00	1>2**
2. Measurement (6 months), $\bar{x}$ (ss)	9.73	0.71			1>3**
3. Measurement (1 year), $\bar{x}$ (ss)	9.78	0.65			1>4**
4. Measurement (2 years), $\bar{x}$ (ss)	9.79	0.77			

Discussion

Studies have shown that the atherogenic index of plasma (AIP) and triglyceride-glucose (TyG) index are new markers for atherosclerosis, insulin resistance, and inflammation, respectively [12, 16]. The TyG index can predict CVD risk in the general population [17]. An elevated TyG index is significantly associated with a higher risk of arterial stiffness [3].

To the best of our knowledge, this is the first study on such a large number of patients with a follow-up period of 2 years to investigate the effects of dapagliflozin, an SGLT2i agent, on the AIP and TyG index, predictors of cardiovascular risks. The results showed a significant difference between the AIP values measured before initiation of dapagliflozin (mean, 0.68; SD, 0.33) and the AIP values measured at month 6 (mean, 0.62; SD, 0.30) ($p < 0.00$). Additionally, we noted a significant difference between the TyG values at baseline (mean, 9.98; SD, 0.76) and the TyG values measured at month 6 (mean, 9.73; SD, 0.71) ($p < 0.00$). These differences lasted and remained significant at 12 and 24 months.

In an animal study, B. Ganbaatar et al. treated diabetic mice using SGLT2i (empagliflozin) for 12 weeks. The drug was shown to lower blood glucose ($p < 0.001$) and lipid levels (triglyceride $p = 0.005$). It significantly reduced atherosclerotic lesion size in the aortic arch through reduction of lipid accumulation ($p < 0.05$), macrophage accumulation ($p < 0.001$), and inflammatory molecule release ($p < 0.01$) in the treatment group compared to the control group [18].

In animal experiments conducted by Y. Liu et al., mice with induced diabetes were given empagliflozin for 12 weeks. The results showed that the drug reduced atherosclerotic lesion burden in the aortic arch (−8.6%, $p = 0.004$). In addition, empagliflozin also led to reductions in body weight (−3.27 g, $p = 0.002$) and lipid profiles (TC: [−15.3 mmol/L, $p = 0.011$]; TG: [−2.4 mmol/L, $p < 0.001$]; LDL: [−2.9 mmol/L, $p = 0.010$]) [19].

A meta-analysis conducted by Ghosh-Swaby et al. with a total of 38,723 participants, including four cardiovascular outcome studies, EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, and CREDENCE, showed that patients who received SGLT2i had 12% lower risk of atherosclerotic MACE (cardiovascular mortality, non-fatal MI, and non-fatal stroke) compared to patients on placebo [hazard ratio, 0.88; 95% confidence interval, 0.82–0.94] [20].

T. Hayashi et al. compared sitagliptin and dapagliflozin and showed that dapagliflozin significantly reduced body weight, systolic blood pressure, plasma triglycerides, and liver transaminases and increased adiponectin. Dapagliflozin did not lead to a change in LDL-C concentrations, but lowered sdLDL-C by 20% and increased lbLDL-C by 18%. It also increased HDL2-C by 18% without affecting HDL3-C. Dapagliflozin decreases sdLDL-C, which has a strong atherogenic potential, and increases HDL2-C, a favorable cardiometabolic marker [19]. In our study, LDL cholesterol decreased by 5% and HDL cholesterol increased by 7%. LDL cholesterol continued to decrease and HDL cholesterol continued to rise at months 12 and 24.

To determine how analysis results were affected by hyperlipidemia medications (statin and/or fenofibrate) which were started before initiation of dapagliflozin, tests for AIP and TyG were repeated among those who did not receive hyperlipidemia treatment; ANOVA findings revealed that the significant correlation persisted at a level of 0·03.

A study from Turkey showed that administration of SGLT2i agents dapagliflozin and empagliflozin resulted in a significant reduction in AIP and TyG indexes at month 6 ($p < 0.01$ with dapagliflozin and $p < 0.05$ with empagliflozin) [21]. These results are in line with our study, which showed that AIP and TyG indexes continued to decrease at months 12 and 24.

In the present study, dapagliflozin was also analyzed for its effects on glycemic control and was found to improve HbA1c and FBG for 24 months; it reduced HbA1c by 0.43% at month 6 and by 0.35% at month 24. It decreased FBG levels by 36 mg/dl at month 6 and by 35 mg/dl at month 24. These results are in line with previous studies from Turkey and other countries [21, 22].

The present study has some limitations: it was a single-center cross-sectional study and thus its results cannot be generalized to the entire population. The study's retrospective nature, single-center setting, and absence of a control group should be considered when interpreting the results. Further research with controlled designs and longer follow-up periods is warranted to confirm the observed effects and their clinical implications. The retrospective design limits the control over variables, potential biases, and the ability to establish causality. Unmeasured confounders could impact the observed effects. Also, as it was a retrospective study, it could not access patient outcomes

for weight and blood pressure before and after treatment. While AIP and TyG indices are relevant markers, the study does not directly assess clinical cardiovascular outcomes, such as myocardial infarction or stroke. The strength of our study is that it is the first real-life study conducted with such a large number of patients, over a long follow-up period covering 24 months.

DM is an increasingly important public health problem that affects quality of life and leads to economic consequences. A number of treatments are being developed to improve quality of life and prevent complications among patients. SGLT2i agents are one of these agents and have been found to have positive effects through reduction of MACEs, CV mortality, HF, and CKD, which are largely of atherosclerotic origin. However, the role of SGLT2i in different ASCVD events remains to be explored more extensively. The precise mechanisms linking SGLT2 to atherosclerotic processes have not yet been fully elucidated. Further high-quality experimental and observational studies with sufficient numbers of patients and follow-up periods are needed to investigate the potential role of SGLT2-i in subclinical atherosclerosis and ASCVD events.

Conclusion

In conclusion, dapagliflozin initiated at the time of diagnosis in patients with type 2 diabetes mellitus lowers the AIP and TyG index, which may help slow down the atherosclerotic process and prevent associated microvascular and macrovascular complications.

Author contribution DENİZ G, SEMRA ÖÖ, and ZEHRA K were involved in original all articles, applying eligibility criteria, and identifying original articles. All authors contributed extensively to manuscript writing, figure and table design, and revision.

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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 clearance This study was approved by Mersin University Non-Interventional Clinical Research Ethics Committee (Decision date/No: 2023/291) and conducted in accordance with the Declaration of Helsinki and Human Rights. Before the survey, participants provided electronic informed consent and were informed of their right to withdraw without explanation.

Informed consent Informed consent was obtained from all the subjects online.

Conflict of interest The authors declare no competing interests.

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