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ORIGINAL ARTICLE

Early effect of exenatide treatment on atherogenicity in patients with type 2 diabetes mellitus

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Abstract

Objective Diabetes mellitus is a chronic metabolic disease often associated with hyperlipidemia. High low-density lipoprotein cholesterol (LDLc), high triglyceride, and low high-density lipoprotein cholesterol (HDLc) form the atherogenic lipoprotein profile. In this study, we examined how exenatide, a glucagon-like peptide 1 (GLP-1) analog, affects lipid profile and atherogenic indices in patients with diabetes.

Methods 100 patients diagnosed with type 2 diabetes mellitus (T2DM) participated in this retrospective study. Clinical and laboratory data of the patients were obtained before exenatide treatment and at the 12th week. From the lipid profile, Atherogenicity Plasma Index (AIP), Castelli Risk Index I (CRI-I), Castelli Risk Index II (CRI-II), Atherogenic Coefficient (AC), triglyceride (TG)/HDLc, TG- Glucose index (TyG) and TyG-Body Mass Index (BMI) data were calculated.

Results There was a significant improvement in body weight (BW), BMI, fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c), and conventional lipid profile after exenatide treatment. Statistically, significant decreases were observed in atherogenicity indices TyG index, TyG-BMI index, CRI-I, CRI-II, AIP, and AC indices ($p < 0.05$). This improvement in TG/HDLc, TyG index, CRI-I, CRI-II, AIP and AC indices was independent of HbA1c and BMI. Especially in patients with BMI ≥ 40 kg/m^2, TyG-BMI index (p:0.01), a statistically significant decrease was observed in TyG index, TyG-BMI index, CRI-I, and AIP values in patients with HbA1c $\geq 8\%$ (p:0.001, p:0.016, p:0.047, p:0.008).

Conclusion In addition to its commonly known effects such as lowering FPG levels and weight loss, exenatide has been observed to have a positive effect on traditional lipid profiles and atherogenicity-related indices. In addition to its antidiabetic effect, it should be considered in diabetic patients in treatment options for atherosclerotic cardiovascular prevention.

Keywords GLP-1 analogs · Exenatide · Type 2 diabetes mellitus · Atherogenicity

Introduction

It is estimated that 450 million individuals worldwide have type 2 diabetes mellitus (T2DM), and by the year 2040, that number will rise to 640 million [1]. The close relationship of T2DM with insulin resistance and obesity has brought a new perspective to treatment in recent years. The insufficient weight loss effect of oral antidiabetic drugs and insulin analogs, which have been in use for a long time, especially in diabetic obese patients, has led to the emergence of glucagon-like peptide-1 (GLP-1) agonist drugs. GLP-1 is a polypeptide hormone released from L cells in the intestinal wall. While GLP-1 inhibits glucagon release from the pancreas, it increases insulin release. As a result, blood sugar control is achieved. In addition to these effects, GLP-1 slows gastric emptying and reduces gastric acid secretion. These effects result in decreased appetite and weight loss [2]. GLP-1 receptor agonist drugs are grouped as short-acting (lixisenatide and exenatide) and long-acting (dulaglutide, liraglutide, albiglutide, and exenatide). In addition, a new glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist drug called tirzepatid has been used in recent years [3, 4]. Among these drugs, exenatide is available in a short-acting form for 2–4 hours (twice a day) and a long-acting form for up to 1 week (once a week) [5, 6].

According to the World Health Organization (WHO) report, overweight and obesity affect 60% of adults in

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European countries. According to this report, obesity has been increasing rapidly over the years in the countries in the region and obesity is not expected to regress in any country until 2025 [7]. Obesity poses a significant risk for the development of T2DM. As a result of BMI exceeding 35 kg/m^2, the risk of developing T2DM increases between 49 and 93 times. Every 1 kg of weight loss in obese individuals reduces the conversion of impaired glucose tolerance to T2DM by approximately 16% [8]. Concomitant hypertension and atherogenic hyperlipidemia in diabetic obese individuals constitute metabolic syndrome (MS). Atherosclerosis in patients with MS is the main cause of cardiovascular morbidity and mortality. Low-density lipoprotein cholesterol (LDLc) is considered the lipoprotein with the highest risk of atherosclerosis. In addition, LDLc is the cholesterol most closely associated with insulin resistance. In recent years, lowering LDLc has been seen as the most important measure for the prevention of atherosclerosis and cardiovascular mortality [9, 10]. While atherosclerosis is best detected by invasive imaging methods, studies on non-invasive atherogenic indices have attracted attention in recent years. Atherogenicity Plasma Index (AIP), Castelli Risk Index I (CRI-I), Castelli Risk Index II (CRI-II), Atherogenic Coefficient (AC), triglyceride (TG)/ high-density lipoprotein cholesterol (HDLc), TG-Glucose index (TyG) and TyG-Body Mass Index (BMI) are some of them [11–14]. In studies, positive effects of GLP-1 agonists on lipid profile and positive effects on atherogenic cardiovascular diseases were investigated with large patient populations through invasive studies [15, 16]. However, the number of studies on non-invasive atherogenic indices of GLP-1 analogs is limited. The early effects of exenatide on new atherogenic indices were investigated in this study.

Material and method

Patient selection

This study was conducted on 100 obese (BMI ≥ 35 kg/m^2) patients diagnosed with T2DM who applied to our hospital between January 2019 and June 2021. The flow chart for patient admission is shown in Fig. 1. Exenatide therapy began with 5 µg subcutaneous (sc) given twice daily, and

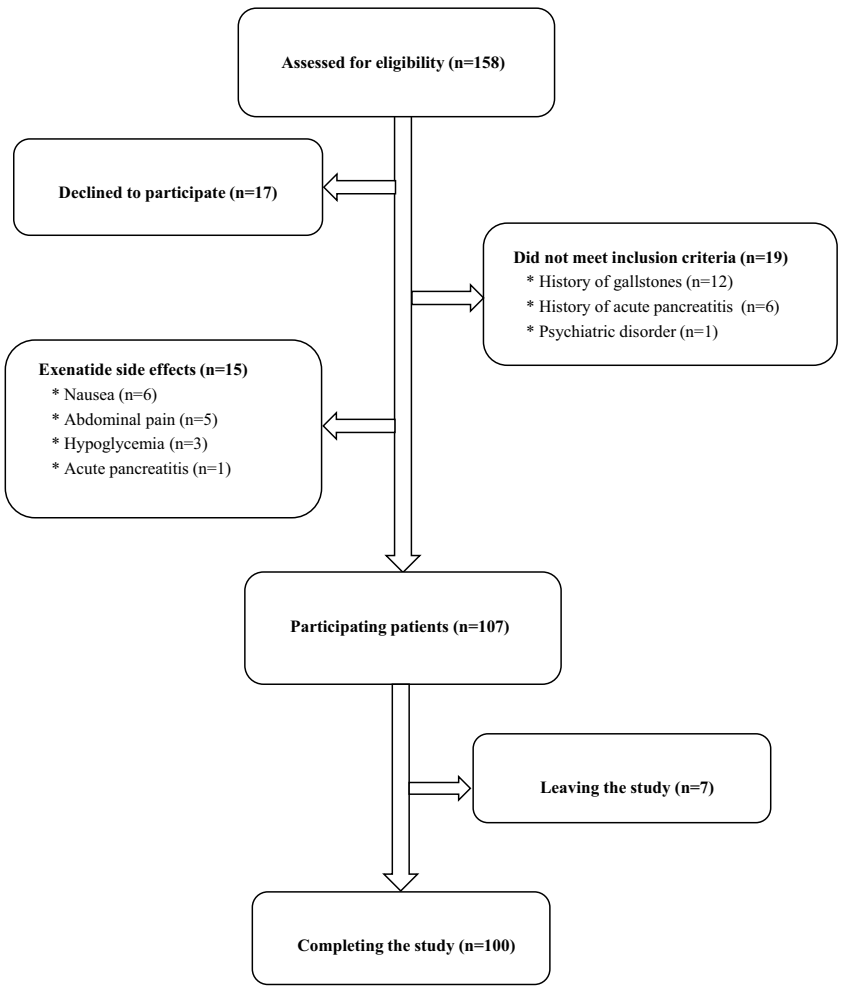

Fig. 1 Flow diagram

after 4 weeks, 10 µg sc twice daily. The examination of the patients was completed at the beginning and the end of 12 weeks.

Patient exclusion criteria

- Volunteers under the age of 18
- Patients with a previous medical history of gallstones
- Patients with a past medical history of acute pancreatitis
- Patients who develop side effects during the use of exenatide and cannot complete the 3-month treatment period (for reasons such as nausea, abdominal pain, and dizziness)
- Patients with psychiatric disorders
- Patients with history of or family history of medullary thyroid carcinoma, patients with multiple endocrine neoplasia syndrome type 2
- Patients with microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (coronary artery disease, cerebrovascular accident, peripheral artery disease) complications
- Patients who declined to contribute for the research

Clinical and biochemical measurements

All patients' ages, genders, and drug regimens were documented at the start of the trial. For all patients, body weight (BW), height, BMI, and biochemical tests were recorded on the hospital database at baseline and 12 weeks. HbA1c test was performed by the HPLC method in the Trinity Biotech device. Biochemical parameters, including FPG, TC, HDL-c, LDL-c, TG, creatinine, AST, ALT and albumin, were measured using the Beckman Coulter AU5800 device. Non-high-density lipoprotein cholesterol (non-HDLc) was calculated with the formula total cholesterol (TC)–HDLc. TyG index was calculated with the formula Ln(fasting TG [mg/dl] x fasting plasma clucose (FPG) [mg/dl])/2. TyG-BMI index was calculated with the formula TyG x BMI. CRI-I was calculated with the formula TC/HDLc. CRI-II was calculated with the formula LDLc/HDLc. AIP was calculated with the formula Log10 (TG/HDLc). AC was calculated with the non-HDLc / HDLc formula.

Statistical analysis

SPSS version 26 application (IBM Corporation) was used to examine the information gathered for our study. The distribution of data was evaluated by Kolmogorov-Smirnov test. In the form of categorical data, numbers (n) and percentages (%) were used. Paired Samples t-test (normal) and Wilcoxon test (non-normal) were used in dependent groups. In the comparison of independent groups, the independent samples t-test was used for data with normal distribution and Mann Whitney U test was used for data not distributed normally. The threshold for statistical significance (P) was set at 0.05. We evaluated the levels of atherogenic indices affected by BMI and HbA1c with multivariate linear regression analysis.

Informed consent

Approval for our research was obtained from the Aksaray University Faculty of Medicine Clinical Research Ethics Committee with the number 2021/08–08. The Declaration of Helsinki of the World Medical Association guided the execution of this study. All participants received signed informed permission after being made aware of the research protocol.

Results

25 (or 25%) of the article's patients were men, and 75 (or 75%) were women. The average patient age was 52.2 year. After 12 weeks of exenatide treatment, major reductions were seen in the BW, BMI, FPG, HbA1c, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) parameters of the patients ($p < 0.001$, $p < 0.001$, p: 0.004, $p < 0.001$, $p < 0.001$, p:0.002). Albumin raised in a meaningful way (p:0.03). Statistically significant decreases were observed in TC, TG, LDLc, and non-HDLc data within the conventional lipid profile (p:0.003, $p < 0.001$, p:0.008, $p < 0.001$). No appreciable alterations were found in the HDL-c data (Table 1). 32 patients included in our study were using one antilipidemic drug and 68 patients were not using antilipidemic drugs. There was no antilipidemic drug change in any patient during the study period. In our study, no statistically significant difference was found in atherogenic index changes (Δ) between patient groups using antilipidemic drugs and those not using antilipidemic drugs ($p > 0.05$). As seen in Table 1 after three months of treatment, atherogenicity indices TG/HDLc ($p < 0.001$), TyG index ($p < 0.001$), TyG-BMI index ($p < 0.001$), CRI-I ($p < 0.001$), CRI- II (p:0.003), AIP ($p < 0.001$) and AC ($p < 0.001$) showed statistically significant decreases. In addition, this improvement in TG/HDLc, TyG index, CRI-I, CRI-II, AIP, and AC indices was found to be independent of HbA1c and BMI (Table 4).

The participants were separated into two categories based on their BMIs, which were < 40 kg/m^2 and ≥ 40 kg/m^2. Statistically significant reductions in BW ($p < 0.001$), BMI ($p < 0.001$), and HbA1c (BMI < 40 kg/m^2; $p < 0.001$, BMI ≥ 40 kg/m^2; p:0.001) parameters in both groups after 12 weeks of exenatide treatment detected. The decrease in FPG was not significant having BMI <40 kg/m^2 (p:0.125), but it was significant having BMI ≥ 40 kg/m^2 (p:0.02). A significant decrease in ALT (BMI < 40 kg/m^2; p:0.037, BMI ≥ 40 kg/m^2; p:0.003) and AST (BMI < 40 kg/m^2;

Table 1 Demographic, clinical data, and atherogenicity indexes

Parameters	Basal	3. month	Δ	*p*
Age (years)	52.2 ± 1			
Weight (kg)	111.1 ± 1.9	102.9 ± 1.9	-8.23 ± 6.37	<0.001*
BMI (kg/m^2)	42.7 ± 0.7	39.4 ± 0.7	-3.35 ± 3.09	<0.001*
FPG (mg/dl)	151.5 (69–393)	134.5 (74–394)	-11.5 (-226–242)	0.004*
HbA1c (%)	7.8 (5.5–13.9)	7 (5-13.4)	-0.6 (-6,6–6,2)	<0.001*
Creatinine (mg/dl)	0.6 ± 0.1	0.7 ± 0.2	0.02 ± 0.14	0.146
ALT (U/L)	21.5 (8–117)	19 (5–69)	-2 (-58–20)	<0.001*
AST (U/L)	20.5 (12–111)	19 (10–58)	-2 (-59–44)	0.002*
Albumin (g/dl)	4.1 ± 0.03	4.2 ± 0.02	0.06 ± 0.3	0.033*
Traditional lipid profile/parameters				
TC (mg/dl)	200.5 (112–367)	183 (86–402)	-4 (-107–94)	0.003*
TG (mg/dl)	172 (73–1295)	141 (52–1063)	-22.5 (-420–292)	<0.001*
LDLc (mg/dl)	121 ± 3.4	112 ± 3.9	-8.96 ± 33.19	0.008*
HDLc (mg/dl)	48.1 ± 1	48.8 ± 1	-0.7 ± 8	0.383
Non–HDLc (mg/dl)	151 (81–318)	134.5 (52–353)	-7.5 (-110–89)	<0.001*
Atherogenicity indexes				
TG/HDLc	3.51 (1.27–26.43)	2.82 (0.78–21.69)	-0.38 (-9.68–8.07)	<0.001*
TyG index	9.50 ± 0.67	9.20 ± 0.67	-0.31 ± 0.68	<0.001*
TyG-BMI index	406.90 ± 69.10	363.50 ± 69.90	-43.48 ± 39.79	<0.001*
CRI-I	4.33 ± 0.984	4.01 ± 0.99	-0.32 ± 0.78	<0.001*
CRI-II	2.51 (1.08–5.8)	2.24 (0.64–4.63)	-0.17 (-2.46–2.37)	0.003*
AIP	0.56 ± 0.253	0.47 ± 0.244	-0.09 ± 0.19	<0.001*
AC	3.33 ± 1.033	3 ± 0.99	-0.34 ± 0.79	<0.001*

* *p* value <0.05 was considered statistically significant

Δ: value change

BMI: Body Mass Index

FPG: Fasting Plasma Glucose

ALT: Alanine aminotransferase

AST: Aspartate aminotransferase

TC: Total cholesterol

TG: Triglyceride

LDLc: Low-density lipoprotein cholesterol

HDLc: High-density lipoprotein cholesterol

Non-HDLc: Non-high density lipoprotein cholesterol

TyG index: TG-Glucose index (TyG)

CRI-I: Castelli Risk Index I

CRI-II: Castelli Risk Index II

AIP: Atherogenicity Plasma Index

AC: Atherogenic Coefficient

p:0.022, BMI ≥ 40 kg/m^2; *p*:0.031) parameters was found after treatment. When the traditional lipid profile was examined, a notable decline was discovered in the TC (*p*:0.005), TG (*p*:0.018), LDLc (*p*:0.028), and Non-HDLc (*p*:0.003) parameters having BMI <40 kg/m^2. Significant reductions in TG ($p < 0.001$) and non-HDLc (*p*:0.02) were found with treatment having BMI ≥40 kg/m^2, but there was no discernible difference in any further metrics. Statistical analysis of TyG index (*p*:0.024), TyG-BMI index ($p < 0.001$), CRI-I (*p*:0.02), AIP (*p*:0.015) and AC (*p*:0.008) parameters having BMI <40 kg/m^2 significant decreases were observed, but no significant changes were found in TG/HDLc and CRI-II parameters. In the group with BMI ≥40 kg/m^2, TG/HDLc ($p < 0.001$), TyG index ($p < 0.001$), TyG-BMI index ($p < 0.001$), CRI-I (*p*:0.005), CRI-II (*p*:0.016), AIP ($p < 0.001$) and AC (*p*:0.01) parameters decreased statistically significantly. Exenatide reduced BW, BMI, and TyG-BMI index, and

these reductions were more pronounced in the group with BMI ≥40 kg/m^2 than in the group with BMI 40 < kg/m^2 (p:0.008, p:0.016, and p:0.01, respectively) (Table 2).

Groups with HbA1c <8% and ≥ 8% were created from all patients. There was a major reduction in BW ($p < 0.001$) and BMI ($p < 0.001$) data after treatment across both groups.

Table 2 Demographic data, clinical data, atherogenic indexes of BMI <40 kg/m^2 and BMI ≥40 kg/m^2 patients

	BMI <40 kg/m^2 (n:45)				BMI ≥40 kg/m^2 (n:55)				p^{Δ}
Parameters	Basal	3. Month	Δ	p	Basal	3. Month	Δ	p	
Age (years)	52.1 ± 10.6				52.3 ± 9.1				
Weight (kg)	98.7 ± 11.96	92.2 ± 12.56	-6.46 ± 3.57	<0.001*	121.3 ± 17.20	111.6 ± 18.72	-9.67 ± 7.7	<0.001*	0.008*
BMI (kg/m^2)	36.6 ± 1.62	34.1 ± 2.27	-2.59 ± 1.43	<0.001*	47.7 ± 6.15	43.7 ± 6.65	-3.97 ± 3.86	<0.001*	0.016*
FPG (mg/dl)	154 (75-393)	141 (74-394)	-12 (-226–242)	0.125	149 (69-359)	129 (78-362)	-7 (-204–158)	0.02*	0.69
HbA1c (%)	8.2 (5.6–13.6)	7.4 (5–11.6)	-0.5 (-6.6–1.4)	<0.001*	7.8 (5.5-13.9)	6.9 (5.2-13.4)	-7 (-5.7–6.2)	0.001*	0.57
Creatinine (mg/dl)	0.65 (0.43-1.38)	0.68 (0.4-1.47)	0.01 (-0.29–0.7)	0.232	0.66 (0.33–1.08)	0.62 (0.38–1.3)	0.01 (-0.44–0.3)	0.44	0.72
ALT (U/L)	21 (8-76)	19 (7-69)	-1 (-23–20)	0.037*	22 (9-117)	19 (5-59)	-2 (-58–18)	0.003*	0.7
AST (U/L)	20 (12–48)	21 (13–111)	-2 (-16–11)	0.022*	21 (13-111)	20 (10-58)	-2 (-59–44)	0.031*	0.88
Albumin (g/dl)	4.13 ± 0.36	4.26 ± 0.21	0.13 ± 0.28	0.005*	4.2 ± 0.26	4.21 ± 0.26	0.01 ± 1.3	0.735	0.06
Traditional lipid profile/parameters									
TC (mg/dl)	196 (128–280)	203 (112–367)	-9 (-103–66)	0.005*	203 (112-367)	188 (116-402)	-2 (-107–94)	0.152	0.23
TG (mg/dl)	183 (73-554)	147 (52-422)	-16 (-420–67)	0.018*	154 (80-1295)	133 (57-1063)	-27 (-363–292)	<0.001*	0.39
LDLc (mg/dl)	119.6 ± 31.74	109.3 ± 37.58	-10.24 ± 30.21	0.028*	122.2 ± 36.11	114.3 ± 39.64	-7.91 ± 35.68	0.106	0.73
HDLc (mg/dl)	47.2 ± 9.26	46.8 ± 8.47	-0.4 ± 7.1	0.707	48.8 ± 10.08	50.4 ± 10.19	1.6 ± 8.6	0.173	0.21
Non-HDLc (mg/dl)	148 (92–274)	132 (52–234)	-8 (-109–65)	0.003*	152 (81-318)	140 (64-353)	-7 (-110–89)	0.02*	0.52
Atherogenic indexes									
TG/HDLc	3.9 (1,5-20.6)	3.2 (0.7-12)	-0.09 (-9.68–3.28)	0.079	3.4 (1.2-26.4)	2.5 (1.2-21.6)	-0.66 (-7.93–8.07)	<0.001*	0.15
TyG index	9.53 (8.14–10.9)	9.4 (8.1–10.4)	-3 (-2.01–0.91)	0.024*	9.37 (8.03-11.49)	9.14 (8.03-11.81)	-0.27 (-2.79–1.19)	<0.001*	0.49
TyG-BMI index	350.7 ± 29.376	317.8 ± 32.659	-32.89 ± 26.67	<0.001*	453 ± 57.298	400.8 ± 70.389	-52.14 ± 46.41	<0.001*	0.01*
CRI-I	4.17 (2.66–7.48)	4 (2.12–6.39)	-1.7 (-2.89–1.35)	0.02*	4.12 (2.76-7.49)	3.94 (2.21-8.2)	-0.29 (-2.27–0.73)	0.005*	0.83
CRI-II	2.61 ± 0.88	2.39 ± 0.903	-0.22 ± 0.77	0.062	2.55 ± 0.735	2.29 ± 0.702	-0.26 ± 0.76	0.016*	0.82
AIP	0.58 ± 0.262	0.51 ± 0.245	-0.07 ± 0.19	0.015*	0.55 ± 0.248	0.44 ± 0.241	-0.11 ± 0.2	<0.001*	0.31
AC	3.17 (1.66–6.48)	3 (1.12–5.39)	-0.26 (-2.89–1.35)	0.01*	3.12 (1.44-6.49)	2.94 (1.21-7.2)	-0.29 (-2.27–1.61)	0.002*	0.99

* p value <0.05 was considered statistically significant

Δ: Value change

p^{Δ}: Statistical significance level of value changes

BMI: Body Mass Index

FPG: Fasting Plasma Glucose

ALT: alanine aminotransferase

AST: aspartate aminotransferase

TC: total cholesterol

TG: triglyceride

LDLc: low-density lipoprotein cholesterol

HDLc: high-density lipoprotein cholesterol

Non-HDLc: Non-high density lipoprotein cholesterol

TyG index: TG-Glucose index (TyG)

CRI-I: Castelli Risk Index I

CRI-II: Castelli Risk Index II

AIP: Atherogenicity Plasma Index

AC: Atherogenic Coefficient

In the group with HbA1c <8%, the level of ALT (p:0.039) and AST (p:0.039) data significantly dropped after treatment, nevertheless, there was no appreciable drop in the FPG and HbA1c values. In the group with HbA1c ≥8%, there was a significant decrease in FPG ($p < 0.001$), HbA1c ($p < 0.001$), ALT (p:0.002) and AST (p:0.021) data. There was a significant decrease in TG (p:0.039) and non-HDLc (p:0.015) in the group with HbA1c <8%, but there was no significant change in TC, HDLc, and LDLc. The decrease in TC (p:0.033), TG ($p < 0.001$), LDLc (p:0.037), and non-HDLc (p:0.005) was statistically significant in the group with HbA1c ≥8%, but there was no significant change in HDLc. When evaluated in terms of atherogenic indices, a significant increase was found in TyG-BMI index ($p < 0.001$), AIP (p:0.046), and AC (p:0.035) in the group with HbA1c <8%, nevertheless, there were no appreciable alterations in TG/HDLc, TyG index, CRI-I, or CRI-II. In the group with HbA1c ≥8%, all atherogenic indices (TG/HDLc $p < 0.001$, TyG index $p < 0.001$, TyG-BMI index $p < 0.001$, CRI-I $p < 0.001$, CRI-II p:0.008, AIP $p < 0.001$ and AC p: 0.001) significantly decreased. Exenatide substantially more effectively reduced FPG, HbA1c, TyG index, TyG-BMI index, CRI-I and AIP in the group with HbA1c ≥8% than in the group with HbA1c <8% ($p < 0.001$, $p < 0.001$, p:0.001, p:0.016, p: 0.047 and p:0.008) (Tables 3 and 4).

Discussion

Our study examined the 12-week short-term outcomes of exenatide in 100 overweight diabetic patients treated at our hospital. An important finding of our study is that treatment with exenatide leads to significant short-term improvements in glycemic parameters and lipid profiles of obese diabetic patients. The most remarkable point of the article is that the improvements in these parameters reduce the atherogenic burden calculated by atherogenic indices. Although studies have not clearly elucidated the mechanism, the lipid-lowering effect of exenatide is evident. Studies focus on the reduction of chylomicron synthesis and stimulation of lipoprotein lipase, which is the main cause of intravascular TG clearance. Some other studies focus on the increase of chylomicron metabolism due to the improvement of insulin sensitivity induced by weight reduction. The decrease in chylomicron synthesis in enterocytes with little or no GLP-1 receptor suggests that there may be other receptors that have not yet been identified. Studies show that the decrease in chylomicron synthesis occurs independently of delayed gastric emptying and increased insulin secretion. In various studies, disruption of lymphatic lipid flow from the thoracic duct or the stimulation of peroxisome proliferator-activated receptor alpha by GLP-1 receptor agonist is thought to decrease TG [15]. It is thought that GLP-1 agonists have some direct cardiovascular effects besides the anti-atherosclerotic effects provided by the improvement in the lipid profile. Some of the mechanisms that produce this effect are to decrease matrix metalloproteinase-2 (MMP-2) levels and inhibit vascular smooth muscle cells. However, studies show conflicting results for cardiovascular effects in the clinical experience of GLP-1 agonists in patients. Despite the contradictions, some of the accepted effects are a reduction in myocardial infarction, a reduction in all-cause cardiovascular mortality, and a reduced risk of stroke. In these investigations, GLP-1 agonists were not linked to a decline in heart failure (HF) [16].

In patients with MS, the atherogenic lipoprotein profile features high LDLc, hypertriglyceridemia, and low HDLc. This profile is closely associated with increased cardiovascular disease (CVD), increased morbidity, and greater mortality in MS patients. In individuals with CVD and T2DM, elevated LDLc seems like an important predictor of cardiovascular events [17]. In a study comparing liraglutide and placebo group, a decreasing trend was found in the TG level in the group using liraglutide, even if it didn't matter. Moreover, the LDLc level substantially increased in this research, although the HDLc level did not alter much [18]. In another study comparing semaglutide with the placebo group, significant decreases were found in TC, TG, VLDL, and HDLc levels in the group using semaglutide [19]. In a study comparing lixisenatide with glargine insulin, lixisenatide was superior for improvement in lipid profile [20]. Similarly, in our study, exenatide provided significant reductions in TC, LDLc, TG and non-HDLc in the early 12-week period in obese patients with T2DM. Exenatide was shown to have a similar effect on lipid profiles in groups with and without adequate blood sugar management. Likewise, the improvement in the lipid profile did not differ in the groups separated by BMI. Results of GLP-1's agonists on cardiovascular adverse events, both through improvement in lipid profile and improvement in direct vascular structure, have been investigated in studies. In the EXSCEL study, no superiority was found over placebo in cardiovascular mortality rates, myocardial infarction, stroke, and hospitalization rates for heart failure in patients using exenatide, but there was no significant difference in safety [21]. In the SUSTAIN-6 study, in the group receiving semaglutide, there was a decrease in non-fatal myocardial infarction and non-fatal stroke, but the risk of cardiovascular death was similar to the placebo group [22]. Liraglutide drastically reduced cardiovascular mortality and all-cause mortality in the LEADER trial participants as compared to the placebo group. In this study, the frequency of hospitalization for myocardial infarction, stroke, and heart failure was insignificantly lower in the liraglutide group compared to the placebo [23]. A study comparing albiglutide with the placebo group showed superiority over placebo for cardiovascular mortality, myocardial infarction,

Table 3 Demographic data, clinical data, atherogenic indexes of HbA1c <8% and HbA1c ≥8% patients

	HbA1c <8% (n:52)				HbA1c ≥8% (n:48)				p^{Δ}
Parameters	Basal	3. Month	Δ	*p*	Basal	3. Month	Δ	*p*	
Age (years)	51.1				53.5				
Weight (kg)	115.5 (80-155)	107.5 (75-149)	-7 (-31–3.8)	<0.001*	101.5 (79-166)	94.1 (74-165)	-7.8 (-43–-1)	<0.001*	0.87
BMI (kg/m^2)	44 ± 8.35	40.6 ±7.89	-3.4 ± 3.49	<0.001*	41.3 ± 5.51	38 ± 5.78	-3.29 ± 2.61	<0.001*	0.82
FPG (mg/dl)	126 (69-319)	122.5 (78-362)	-1.5 (-183–158)	0.831	196 (100-393)	152 (74-394)	-45 (-226–242)	<0.001*	<0.001*
HbA1c (%)	6.8 (5.5-7.9)	6.5 (5-13.4)	-0.1 (-2.2–6.2)	0.451	9.5 (8–13.9)	7.9 (5.3–13.1)	-1.45 (-6.6–1.1)	<0.001*	<0.001*
Creatinine (mg/dl)	0.67 (0.33-1.38)	0.67 (0.38-1.47)	-0.03 (-0.44–0.3)	0.242	0.63 (0.38–1.08)	0.61 (0.38–1.34)	0.01 (-0.29–0.7)	0.33	0.86
ALT (U/L)	22.5 (10-117)	19.5 (5-69)	-2 (-58–20)	0.039*	20.5 (8-76)	17 (7-55)	-1.5 (-36–17)	0.002*	0.43
AST (U/L)	21.5 (13-111)	19.5 (13-52)	-2 (-59–11)	0.039*	19 (12-48)	19 (10-58)	-2 (-17–44)	0.021*	0.66
Albumin (g/dl)	4.2 (3-4.8)	4.28 (3.5-4.9)	-0.1 (-0.89–0.82)	0.153	4.2 (3.3–4.9)	4.28 (3.6–4.7)	0.06 (-0.35–1.1)	0.04*	0.92
Traditional lipid profile/parameters									
TC (mg/dl)	198 (128–288)	186.5 (116–303)	-5 (-82–94)	0.04*	204,5 (112-367)	182,5 (86-402)	-3.5 (-107–54)	0,033*	0.82
TG (mg/dl)	153.5 (73–465)	144.5 (57–298)	-8.5 (-338–67)	0.07	185,5 (73-465)	136,5 (52-1063)	-30 (-420–292)	<0,001*	0.008
LDLc (mg/dl)	120,3 ± 28,77	113,8 ± 36,19	-6.5 ± 28.69	0,108	121,8 ± 39,31	110,2 ± 41,38	-11.63 ± 37.6	0,037*	0.44
HDLc (mg/dl)	50,1 ± 8,69	50,1 ± 9,83	0.04 ± 8.56	0,974	45,9 ± 10,36	47,3 ± 9,19	1.42 ± 7.33	0,187	0.39
Non-HDLc (mg/dl)	148.5 (85–274)	137 (74–222)	-9.5 (-99–89)	0.01*	159 (81-318)	133.5 (52-353)	-6.5 (-110–35)	0.005*	0.99
Atherogenic indexes									
TG/HDLc	3.18 (1.27-10.57)	2.75 (1.38-8.7)	-0.07 (-6.83–3.28)	0.135	3.98 (1.55-26.43)	2.86 (0.78-21.69)	-0.85 (-9.68–8.07)	<0.001*	0.006
TyG index	9.19 ± 0.467	9.09 ± 0.534	-0.1 ± 0.59	0.242	9.9 ± 0.663	9.35 ± 0.765	-0.55 ± 0.7	<0.001*	0.001*
TyG-BMI index	404.5 ± 75.911	370.1 ± 76.461	-34.37 ± 40.75	<0.001*	409.6 ± 61.782	356.3 ± 62.221	-53.35 ± 36.63	<0.001*	0.016*
CRI-I	4.11 ± 0.795	3.94 ± 0.887	-0.17 ± 0.69	0.081	4.56 ± 1.114	4.09 ± 1.095	-0.48 ± 0.84	<0.001*	0.047*
CRI-II	2.44 ± 0.623	2.32 ± 0.736	-0.12 ± 0.58	0.132	2.72 ± 0.941	2.36 ± 0.863	-0.37 ± 0.91	0.008*	0.12
AIP	0.49 ± 0.197	0.44 ± 0.189	-0.04 ± 0.16	0.046*	0.64 ± 0.283	0.5 ± 0.292	-0.15 ± 0.22	<0.001*	0.008*
AC	3.03 (1.44–6.09)	2.85 (1.12–5.39)	-0.17 (-2.12–1.61)	0.02*	3.43 (1.76-6.49)	3.03 (1.21-7.2)	-0.4 (-2.89–0.8)	0.001*	0.17

* p value <0.05 was considered statistically significant

Δ: Value change

p^{Δ}: Statistical significance level of value changes

BMI: Body Mass Index

FPG: Fasting Plasma Glucose

ALT: Alanine aminotransferase

AST: Aspartate aminotransferase

TC: Total cholesterol

TG: Triglyceride

LDLc: Low-density lipoprotein cholesterol

HDLc: High-density lipoprotein cholesterol

Non-HDLc: Non-high density lipoprotein cholesterol

TyG index: TG-Glucose index (TyG)

CRI-I: Castelli Risk Index I

CRI-II: Castelli Risk Index II

AIP: Atherogenicity Plasma Index

AC: Atherogenic Coefficient

and stroke. This study also emphasized that albiglutide is not inferior to placebo in terms of safety [24]. The common conclusion of these studies is that GLP-1 agonists do not differ from placebo in cardiovascular safety. On the other hand, positive results have been obtained in cardiovascular adverse events, but not all results support each other.

Table 4 The multivariate linear regression analysis of atherohenic indexes

		Adj. R^2	SC β	t	*p*	95% CI		VIF
						LB	UB	
Δ TG/HDLc	Δ BMI	0.058	-0.162	-0.806	0.422	-0.426	0.180	4.228
	Δ HbA1c		0.085	0,679	0.499	-0.198	0.404	1.645
Δ TyG index	Δ BMI	0.626	0.010	0.082	0.934	-0.053	0.057	4.228
	Δ HbA1c		0.034	0.432	0.666	-0.043	0.066	1.645
Δ TyG-BMI index	Δ BMI	0.813	0.660	15.058	<0.001	7.389	9.633	1.019
	Δ HbA1c		0.042	0.779	0.438	-1.336	3.060	1.546
Δ CRI-I	Δ BMI	0.029	-0.072	-0.722	0.472	-0.068	0.032	1.019
	Δ HbA1c		0.068	0.555	0.580	-0.070	0.125	1.546
Δ CRI-II	Δ BMI	0.004	-0.108	-1.065	0.290	-0.076	0.023	1.019
	Δ HbA1c		0.061	0.486	0.628	-0.073	0.121	1.546
Δ AIP	Δ BMI	0.136	-0.100	-1.058	0.293	-0.018	0.005	1.019
	Δ HbA1c		0.093	0.799	0.426	-0.014	0.032	1.546
Δ AC	Δ BMI	0.063	-0.125	-1.273	0.206	-0.082	0.018	1.019
	Δ HbA1c		0.017	0.137	0.891	-0.091	0.105	1.546

Adj. $R^{2:}$ Adjusted R Spuare
SC β: Standardized Coefficients Beta
95% CI: Confidence interval
LB: Lower bound
UB: Upper bound
VIF: Variance inflation factor
Δ: Value change
BMI: Body Mass Index
FPG: Fasting Plasma Glucose
TyG index: TG-Glucose index
CRI-I: Castelli Risk Index I
CRI-II: Castelli Risk Index II
AIP: Atherogenicity Plasma Index
AC: Atherogenic Coefficient

Cardiovascular mortality is mostly attributed to atherosclerotic heart disease. It is necessary to identify asymptomatic patients at risk for atherosclerosis before encountering the negative consequences of atherosclerotic disease. Some atherogenic indices have been put forward to reveal this risky patient group [13]. In a study conducted to investigate some of these indices, it was shown that the CRI-I, CRI-II, AIP, and AC indices, which are thought to predict atherogenicity among individuals with coronary artery disease that has been diagnosed by angiogram, were significantly higher than the healthy control group [25]. In a study with ApoE-deficient experimental mice, vascular endothelial aging and atherosclerotic plaque growth were detected in mice exposed to chronic stress. A significant reduction in plaque lipid accumulation and atherosclerotic lesion formation was found in chronically stressed mice administered a GLP-1 agonist, exenatide, compared to chronically stressed mice not administered exenatide [26]. In another study, a significantly higher reduction in carotid intima-media thickness (with Doppler ultrasonography) was noted in the patient population receiving the GLP-1 analog liraglutide treatment, independent of the improvement in BW, BMI, and lipid profile, compared to the control group. Thus, the regression of atherosclerosis was demonstrated with liraglutide treatment [27]. Significant regressions were observed in all of the TG/HDLc, TyG index, TyG-BMI index, CRI-I, CRI-II, AIP, and AC atherogenic indices including in our study after exenatide treatment. Morover, exenatide treatment revealed a significant difference in atherogenicity reduction in the BMI $40 \geq kg/m^2$ group compared to the BMI $40 < kg/m^2$ group. Similarly, atherogenic index change due to exenatide treatment was more successful in patients with HbA1c ≥8% than in patients with HbA1c <8%.

Limitations

The minimal number of volunteer patients necessitated the single-centered and retrospective nature of our investigation. This circumstance constrains the findings of our

investigation. Patients without microvascular and macrovascular complications were included in our study. Since it was a retrospective study, invasive atherogenic imaging was not performed because it was not indicated for our patients. The control group was not included in our study because our research plan was designed according to the changes in the pre-treatment and post-treatment times. In this study, we examined the short-term effects of exenatide on atherogenicity indices. Therefore, this study gives limited results about the atherogenic changes that develop in the chronic period. There is a need for randomized controlled studies that include prospective invasive and non-invasive atherogenic parameters and evaluated in terms of cardiac event outcomes in long-term follow-up.

Conclusions

In conclusion, the GLP-1 analog exenatide caused a significant reduction in atherogenicity indices defined in the literature. Exenatide showed these positive effects more prominently having HbA1c ≥8%. Given the elevated risk of cardiovascular problems in obese individuals with uncontrolled diabetes, it is advised to use GLP-1 analogs early on. Our findings should be substantiated by randomized controlled prospective trials in which imaging techniques and invasive procedures can verify exenatide's beneficial effects on atherogenicity.

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Declarations

Ethics clearance This study was approved by the Aksaray University Faculty of Medicine clinical research ethics committee (Date: 19.08.2021, Decision no: 2021/08-08). The Declaration of Helsinki (1964) of the World Medical Association guided the execution of this study.

Conflict of interest The authors have no conflict of interest to declare regarding the content of this article.

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