The Effect of GLP-1 Agonist Treatment On Subclinical Atherosclerosis

GLP-1 Agonist Tedavisinin Subklinik Ateroskleroz Üzerine Etkisi

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Abstract

Introduction: Although GLP-1 agonists have been shown to reduce cardiovascular events, their effect on the progression of subclinical atherosclerosis is not clear. In this respect, it was planned to evaluate cardiovascular risk markers in obese and diabetic patients receiving exenatide therapy.

Materials and Methods: This retrospective study included 56 patients with Type 2 Diabetes Mellitus (DM) by body mass index (BMI) >35. Demographic, anthropometric and clinical characteristics before and after six-month treatment with exenatide were screened. Cardiovascular risk marker Atherogenic Index of Plasma (AIP), uric acid, carotis intima media thickness (CIMT), HbA1c, fasting blood glucose (FBG) and postprandial blood glucose (TCG) levels were evaluated.

Results: Eleven of the fifty-six patients had discontinued exenatide due to side effects, etc. 45 patients (35 females, 10 males; age 50 ± 9.5 years) completed the study. AIP, HbA1c, uric acid, fasting plasma glucose, postprandial glucose, waist circumference, hip circumference, body mass index (BMI), total cholesterol, and triglyceride levels were improved with exenatide treatment. However, no change was detected in CIMT, blood pressure, spot urine albumin/creatinine ratio, LDL, and HDL levels.

Conclusion: Glycemic parameters, AIP and uric acid levels, which are biochemical predictors of subclinical atherosclerosis, were improved with GLP-1 agonist exenatide treatment. However, no change was observed in CIMT measurements. These findings can be interpreted as exenatide therapy, can slow down the progression of subclinical atherosclerosis, but has no effect on existing atherosclerotic plaque.

Keywords: Exenatide; incretin; atherosclerosis; diabetes mellitus; cardiovascular risk; obesity.

Introduction

The coexistence of diabetes mellitus (DM) and obesity is known to increase cardiovascular risks. Therefore, the monitoring of cardiovascular markers is crucial. The Atherogenic Index of
Plasma (AIP), serum uric acid and carotid intima media thickness (CIMT) are some of these cardiovascular markers. AIP has been shown to be a strong predictor of atherosclerosis and coronary heart disease risk (1,2), which reflects the relationship between non-atherogenic and atherogenic lipoprotein level and correlates with lipoprotein particle size (2,3). Uric acid is one of the leading indicators of cardiovascular diseases (4). High uric acid levels are considered an independent risk factor for atherosclerosis and cardiovascular events (5). CIMT has recently been used as a non-invasive indicator of the development of atherosclerosis, and studies have reported that increased CIMT is a strong predictor of the risk of stroke, myocardial infarction, and cardiovascular death (6). When planning DM treatment, weight control and cardioprotective efficiency should be targeted in addition to optimal glycemic control. In this respect, glucagon-like peptide-1 (GLP-1) agonist therapies targeting multiple cardiovascular risk factors simultaneously can be considered a good option (7,8). GLP-1 agonists have been shown to have beneficial effects on inflammation, endothelial function, and cardiovascular disease (9–11). Although it has been claimed that at least part of the cardioprotective effect of GLP-1 agonist treatments is due to slowing the progression of atherosclerosis, it has not been conclusively demonstrated in clinical studies (12–17). Exenatide is a short-acting GLP-1 analog that increases glucose-dependent insulin secretion. In this respect, this real-life study was planned to evaluate the effects of exenatide treatment, on cardiovascular markers as well as metabolic control.

Materials and Methods

Patients: This retrospective study was conducted with 56 diabetic patients for whom exenatide treatment was initiated. The study was approved by the Ankara Dişkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee (date: 27/11/2017 number: 43/27). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The patients included were over the age of 18 years, were taking at least two antidiabetic treatment agents, and had a body mass index (BMI) over 35. Diabetic diet and regular exercise were recommended to all patients. The patients were monitored by a dietitian every three months. Exenatide at a dose of 5 μg twice a day was started for all patients, and after one month, the dose was increased to 10 μg twice daily. Four (7.2%) patients were excluded from the study as they did not attend follow-up visits. A total of seven patients discontinued exenatide treatment: one due to drug eruption (1.8%), one due to abdominal pain (1.8%), one due to angioedema (1.8%), one due to diarrhea (1.8%), one due to fatigue (1.8%), and two (3.6%) due to high blood glucose/need for insulin therapy/cost (Figure 1).

Figure 1. Study flow diagram

Clinical and Biochemical Measurements: The clinical and laboratory characteristics of the patients were scanned. Demographic data, comorbidities, complications and antidiabetic drugs used were recorded. The weight, height, and BMI of all patients were measured before the exenatide treatment and after six months. Biochemical examinations were performed before
### Table 1: Demographic characteristics and comorbidities of patients

| Demographic features                                      |          |
|-----------------------------------------------------------|----------|
| Age (years) (mean±st deviation)                           | 50±9.50  |
| Sex (Female/Male) (n (%))                                 | 35/10 (77.8/22.2) |
| Diabetes Mellitus duration (years) (median (min-max))     | 9 (1-30) |

| Comorbidities                                             |          |
|-----------------------------------------------------------|----------|
| Hypertension (n (%))                                      | 26 (62.2) |
| Hyperlipidemia (n (%))                                    | 22 (48.9) |
| Atherosclerotic Heart Disease (n (%))                     | 8 (17.8)  |
| Cerebrovascular Event (n (%))                             | 1 (2.2)   |
| Peripheral Artery Disease (n (%))                         | 1 (2.2)   |

| Complications                                             |          |
|-----------------------------------------------------------|----------|
| Retinopathy (n (%))                                       | 12 (36.4) |
| Nephropathy (n (%))                                       | 9 (27.3)  |
| Neuropathy (n (%))                                        | 15 (45.5) |

### Table 2: Status of drugs used with exenatide therapy

| Medications      | N   | (%)  |
|------------------|-----|------|
| Metformin        |     |      |
| Using            | 3   | (6.6)|
| Not using        | 42  | (93.4)|
| Gliclazide       |     |      |
| Not using        | 28  | (62.2)|
| 30 mg            | 7   | (15.5)|
| 60 mg            | 5   | (11.1)|
| 90 mg            | 2   | (4.4)|
| 120 mg           | 3   | (6.7)|
| Repaglinide      |     |      |
| Not using        | 40  | (88.9)|
| 1.5 mg           | 2   | (4.4)|
| 3 mg             | 1   | (2.2)|
| 8 mg             | 2   | (4.4)|
| Nateglinide      |     |      |
| Not using        | 42  | (93.3)|
| 240 mg           | -   |      |
| 360 mg           | 3   | (6.7)|
| Insulin Dosage   |     |      |
| Not using        | 20  | (44.4)|
| 8-26 Units       | 8   | (17.8)|
| 30-46 Units      | 6   | (13.3)|
| 56-88 Units      | 6   | (13.3)|
Table 3: Laboratory and anthropometric changes with exenatide treatment

| Parameter                                | Pre-exenatide     | Sixth month of exenatide | p     |
|------------------------------------------|-------------------|--------------------------|-------|
| Weight (kg)                              | 107.16±15.79      | 99.11±13.44              | 0.001 |
| BMI (kg/m\(^2\))                         | 41.76±5.49        | 39.74±3.89               | 0.001 |
| Waist circumference (cm)                 | 125.07±9.66       | 118.8±9.05               | 0.001 |
| Hip circumference (cm)                   | 128.05±10.38      | 123.77±6.80              | 0.001 |
| Waist/ Hip Ratio                         | 0.98 ± 0.08       | 0.96 ± 0.06              | 0.061 |
| Systolic Blood Pressure (mmHg)           | 128.82±21.53      | 130.75±6.84              | 0.273 |
| Diastolic Blood Pressure (mmHg)          | 78.96±8.41        | 78.12±2.80               | 0.840 |
| HbA1c (%)                                | 9.26±1.48         | 8.31±1.64                | 0.001 |
| Fasting plasma glucose (mg/dl)           | 189.00 [112.0-401.0] | 172.66 [65.0-310.0]     | 0.023 |
| Postprandial glucose (mg/dl)             | 299.14 [141-516]  | 266.91 [113-501]         | 0.003 |
| Uric acid (mg/dl)                        | 7.84±1.92         | 6.24 ± 0.99              | 0.024 |
| Creatinine (mg/dl)                       | 0.87±0.18         | 0.86±0.16                | 0.738 |
| Spot urine Albumin/ Creatinine (g/mg)    | 20.00 [2.54-2372.0] | 16.0 [2.3-1367.0]       | 0.066 |
| Total cholesterol (mg/dl)                | 197.96±40.39      | 173.71±20.73             | 0.001 |
| LDL (mg/dl)                              | 131.92 ± 29.59    | 133.31 ± 27.18           | 0.416 |
| Triglyceride (mg/dl)                     | 218.0 [63.0-1203.0] | 169.0 [63.0-1203.0]     | 0.016 |
| HDL (mg/dl)                              | 39.77±6.57        | 41.40±4.96               | 0.083 |
| CIMT (mm)                                | 0.69±0.11         | 0.66±0.09                | 0.358 |
| AIP                                       | 0.75±0.04         | 0.65±0.03                | 0.020 |

BMI: body-mass index, LDL: low density lipoprotein, HDL: high density lipoprotein, CIMT: carotis intima-media thickness, AIP: atherogenic index of plasma

and after the treatment, including uric acid, spot urine albumin/creatin ratio, fasting plasma glucose (FPG), post-prandial glucose (PPG), glycated haemoglobin (HbA1c), total cholesterol, high density lipoprotein (HDL), low density lipoprotein, and triglycerides. The cardiovascular risk marker Atherogenic Index of Plasma (AIP), which was obtained by calculating the triglyceride/HDL ratio logarithmically, was measured before and after six months of exenatide treatment (1). Due to obese and diabetic patients are at high cardiovascular risk, CIMT measurement was performed (18). CIMT was measured for the assessment of subclinical atherosclerosis and refine cardiovascular risk stratification of all participants, before and after the exenatide treatment. Measurements were made with 13 MHz high resolution B-mode ultrasound (EUB 7000 HV; Hitachi, Tokyo, Japan) using a linear probe. Three measurements were made from 1 cm proximal of both right and left common carotid artery bifurcations. The distance between posterior wall lumen echogenicity and media-adventitia echogenicity was measured only from the posterior wall. CIMT was calculated from the mean of three measurements in both arteries.

**Statistical Analysis:** The parametric distribution was determined using the Kolmogorov-Smirnov test. Parametric variables were stated as mean±standard deviation values, non-parametric distributed numerical variables as median and range values, and categorical data as number (n) and percentage (%). The parameters were compared from pre-treatment to sixth months using the Paired Samples t test for parametric variables and the Wilcoxon test for non-parametric variables. The difference was determined by subtracting the baseline value from the post-exenatide treatment value. Pearson’s analyses were used for correlations. A value of p<0.05 was assumed for statistical significance.

**Results**
Evaluation was made of 35 (77.8%) female and 10 (22.8%) male patients with a mean age of 50 ± 9.5 years. Duration of diabetes was 9 (1-30) years. Hypertension was determined in 26 (62.2%)
patients, hyperlipidemia in 22 (48.9%) patients, atherosclerotic heart disease in 8 (17.8%) patients, cerebrovascular disease in one (2.2%) patient, and peripheral arterial disease in one (2.2%) patient in whom exenatide treatment was initiated (Table 1). There was no change in the number of patients using metformin in the sixth month of exenatide treatment. Patients on exenatide therapy together with oral anti-diabetic and insulin treatments are shown in Table 2. AIP was measured as 0.75±0.04 before exenatide treatment and as 0.65±0.03 in the 6th month of exenatide treatment. The difference between AIP levels was statistically significant (p=0.020). Uric acid levels decreased from 7.84±1.92 mg/dl to 6.24±0.99 mg/dl with exenatide treatment (p=0.024). CIMT was 0.69±0.11 mm pre-exenatide and 0.66±0.09 mm post-exenatide (p=0.358). Significant changes were detected in HbA1c, fasting plasma glucose, post-prandial glucose, waist circumference, hip circumference, body mass index (BMI), total cholesterol and triglyceride values. No change was detected in blood pressure, spot urine albumin/creatinine ratio, waist/hip ratio, arterial blood pressure, low density lipoprotein and high density lipoprotein levels (Table 3). A significant correlation was found between uric acid levels and AIP both before and after treatment (pre-treatment r=0.405 p=0.006; post-treatment r=0.349 p=0.020). A significant decrease was detected in AIP values with treatment. CIMT values were found to be higher in patients with less uric acid level reduction (r=-0.553, p<0.001). It was determined that the decrease in AIP was correlated with the decrease in HbA1c, but not with weight loss (r=0.303 p=0.043; r=0.267 p=0.076, respectively).

**Discussion**

To assess whether GLP-1 agonists slow the progression of atherosclerosis in DM, this real-life study was conducted evaluating the six-month progression of patients who received exenatide. Improvements were detected in anthropometric measurements. It was observed that the patients lost an average of 8 kg, and parallel to this, improvements were observed in glycemic parameters, uric acid and AIP levels. No statistically significant difference was found between CIMT values before and after exenatide treatment. Previous studies have suggested that GLP-1 agonist therapy may protect against atherosclerosis and cardiovascular disease through its effects on risk factors such as hyperglycemia, obesity, hypertension, and dyslipidemia (7,8). In clinical studies conducted in recent years, neutral or minimal efficacy in plasma lipids and blood pressure has been detected with GLP-1 agonist treatment (9,19–21). In the current study, although there was an improvement in triglyceride and total cholesterol levels, there was no change in blood pressure. This supports the thesis that the cardioprotective effect of GLP-1 agonist treatment is due to the effect of multiple mechanisms (22). In recent years, studies have been published that have failed to show evidence of slowing the progression of atherosclerosis, altering plaque composition, or reducing CIMT, despite improvement in glycemic profile and lipid parameters (23,24). There are also studies in the literature in which CIMT has been shown to decrease with GLP-1 agonist treatment (12,13). The main difference between this study and studies that have found a decrease in CIMT is that the pre-treatment CIMT levels were higher in other studies. Similar to CIMT, non-invasive imaging methods are also available for the evaluation of atherosclerosis and endothelial dysfunction. Flow-mediated vasodilation of the brachial artery and magnetic resonance imaging of the carotid artery wall may provide an appropriate assessment (12,25,26). Magnetic resonance imaging, in particular, has been shown to be more consistently associated with CVD, particularly strokes, compared with CIMT (27). Since this was a retrospective real-life study, magnetic resonance imaging and flow-mediated vasodilatation of brachial artery were not evaluated. More sensitive evaluation can be made with effective imaging such as magnetic resonance imaging and flow-mediated vasodilation of the brachial artery in prospectively designed large-participant studies. It has been reported that AIP plays a predictive role for atherosclerosis and can be used to evaluate cardiovascular risk factors and predict acute coronary events (2). In the current study, AIP decreased significantly with exenatide treatment. This is the first study in the literature to have evaluated the level of AIP with exenatide treatment. AIP reduction was determined to be correlated with HbA1c reduction, but not with weight loss, and a correlation was also found between AIP and uric acid levels. This is in line with other previous studies (28). In addition, although some studies have shown no change in uric acid level with exenatide treatment, the results of the current study showed that uric acid levels decreased with exenatide treatment (29). This may have been due to the higher uric acid level in this study. This study has some limitations. Some data may have been overlooked because it was made by scanning the data of patients followed up in...
routine outpatient clinic conditions. In addition, the high rate of patients excluded from the study may also have affected the results. The absence of a control group can also be said to be a limitation. Finally, due to the nature of the study, a cause-effect relationship could not be established. Nevertheless, this study confirms the need for larger prospective studies to determine the mechanisms underlying the relationship between serum uric acid, AIP, and atherosclerosis.

Conclusion

In conclusion, glycemic parameters, AIP, and uric acid levels, which are biochemical predictors of subclinical atherosclerosis, were improved with exenatide treatment. With treatment, patients lost weight and their BMI decreased. However, no change was observed in CIMT measurements. These results can be interpreted as GLP-1 agonist therapy, the efficacy of which has been shown in cardiovascular outcome studies, can slow down the progression of subclinical atherosclerosis, but has no effect on existing atherosclerotic plaque according to the CIMT measurements. Further studies with more effective imaging modalities than CIMT can be performed to confirm this thesis.

Ethical Approval: The study was approved by the Ethics Committee of our institute (date: 27/11/2017 number: 43/27). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all cases.

Conflict of Interests: The authors have no conflict of interests to declare fort his study.

Financial Support: The study received no financial support.

Authors Contributions: Conceived and designed the study: DS, MES, MB, MK, MO, EC; developed the study protocol, collected the data: all authors; analyzed and interpreted the data: all authors; supervised the study: BU, IOU, MO, EC; Literature search: DS, MC, MES, MB, MK, BU, IUO, MO; main author: DS

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