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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) with a body mass index (BMI) >35. Demographic, anthropometric and clinic 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 (FBS) 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 exetide 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.

Özet

Amaç: Obez ve diyabetik hastalarda kardiyovasküler riskler artmıştır. Bu nedenle, antidiyabetik tedavilerin kardiyovasküler risk üzerine etkileri önemlidir. GLP-1 analoglarının kardiyovasküler olayları azalttığı gösterilmişse de subklinik aterosklerozun progresyonuna etkisi net değildir. Bu açıdan, kliniğimizde eksenatid tedavisi almış hastaların kardiyovasküler risk belirteçlerinin değerlendirilmesini planladık.

Gereç ve Yöntem: Vücut kitle indeksi >35 olan, 56 Tip 2 Diabetes Mellitus (DM) hastasının verileri retrospektif olarak incelendi. Eksenatid tedavisi öncesi ve altı aylık tedavi sonrası demografik, antropometrik ve klinik bulguları tarandı. Trigliserid/HDL oranının logaritmik hesaplanması ile elde edilmiş olan kardiyovasküler risk belirteci Atherogenic Index of Plasma (AIP), ürik asit, carotis intima media kalınlığı (KIMK), HbA1c, açlık kan şekeri (AKŞ) ve tokluk kan şekeri (TKŞ) düzeyleri değerlendirildi.

Bulgular: Elli altı hastanın 11'i yan etki vb. nedenlerle exenatide tedavisini bıraktı. Çalışmaya dahil edilen 45 hastanın AIP, HbA1c, ürik asit, AKŞ, TKŞ, bel çevresi, kalça çevresi, vücut kitle indeksi (VKI), total kolesterol ve trigliserid değerlerinde anlamlı derecede düzelme tespit edildi. Ancak KIMK, kan basıncı, spot idrar albumin/kreatinin oranı, LDL, HDL ve c-peptid düzeylerinde değişiklik tespit edilmedi.

Sonuç: Subklinik aterosklerozun biyokimyasal belirleyicileri olan AIP ve ürik asit düzeylerinde eksenatid tedavisi ile düzelme sağlandı. Ancak KIMK ölçümlerinde herhangi bir değişiklik gözlenmedi. Bu sonuçlar, kardiyovasküler çalışmalarda olumlu etkileri gösterilen GLP-1 agonist tedavisinin subklinik aterosklerozun ilerlemesini yavaşlatabileceği, ancak mevcut aterosklerotik plak üzerinde etkisi olmadığı şeklinde yorumlanabilir.

Anahtar Kelimeler: Eksenatid; inkretin; ateroskleroz; diabetes mellitus; kardiyovasküler risk; obezite.

Introducion

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

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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 Dışkapı 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).

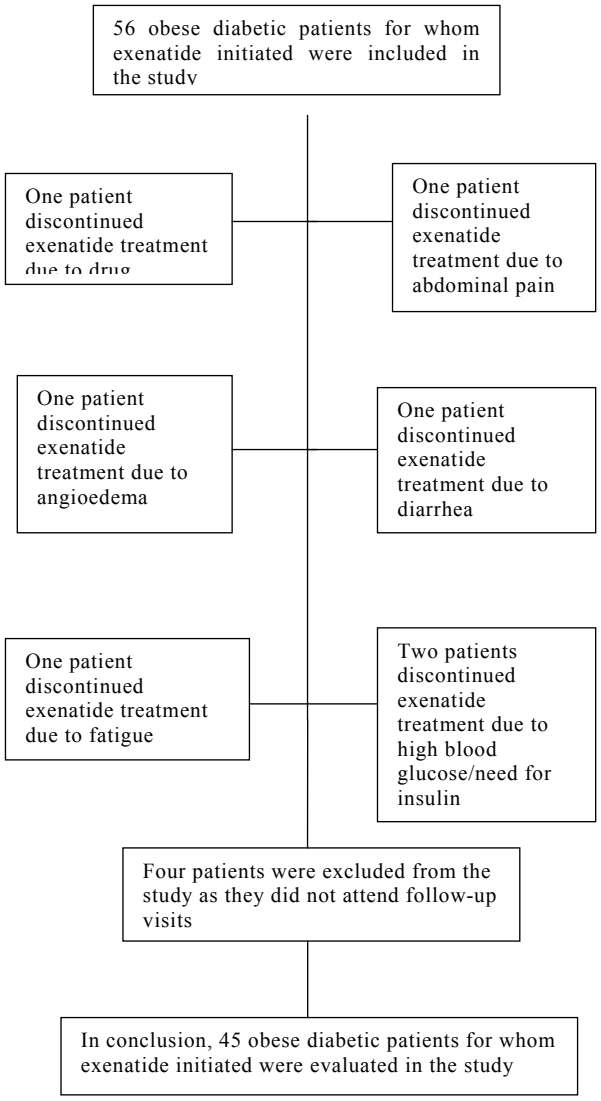

Figure 1. Study flow diagram

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/m2)	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 lipoprotei**n, CIMT:** carotis intima-media thickness, **AIP:** atherogenic index of plasma

and after the treatment, including uric acid, spot urine albümin/creatinin 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 risc stratificataion 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

Evalution 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 antidiabetic 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.

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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

References

1. Dobiášová M, Frohlich J. The plasma parameter log (TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate inapob-lipoprotein-depleted plasma (FERHDL). Clin Biochem 2001; 34(7): 583-588.
2. Dobiášová M, Frohlich J, Šedová M, Cheung MC, Brown BG. Cholesterol esterification and atherogenic index of plasma correlate with lipoprotein size and findings on coronary angiography. J Lipid Res 2011; 52(3): 566-571.
3. Niroumand S, Khajedaluee M, Khadem-Rezaiyan M, Abrishami M, Juya M, Khodaee G, et al. Atherogenic Index of Plasma (AIP): A marker of cardiovascular disease. Med J Islam Repub Iran 2015; 29(1): 240.
4. Tanaka K, Kabayama M, Sugimoto K, Akasaka H, Takami Y, Takeya Y, et al. Association between uric acid and atherosclerosis in community-dwelling older people: The SONIC study. Geriatr Gerontol Int 2021; 21(1): 94-101.
5. Baliarsingh S, Sharma N, Mukherjee R. Serum uric acid: marker for atherosclerosis as it is positively associated with "atherogenic index of plasma." Arch Physiol Biochem 2013; 119(1): 27-31.
6. Peters SA, Grobbee DE, Bots ML. Carotid intima–media thickness: a suitable alternative for cardiovascular risk as outcome? Eur J Cardiovasc Prev Rehabil 2011; 18(2): 167-174.
7. Bunck MC, Diamant M, Eliasson B, Cornér A, Shaginian RM, Heine RJ, et al. Exenatide Affects Circulating Cardiovascular Risk Biomarkers Independently of Changes in Body Composition. Diabetes Care 2010; 33(8): 1734-1737.
8. Robinson LE, Holt TA, Rees K, Randeva HS, O'Hare JP. Effects of exenatide and liraglutide on heart rate, blood pressure and body weight: systematic review and meta-analysis. BMJ Open 2013; 3(1): e001986.
9. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2016; 375(4): 311-322.
10. Koska J, Sands M, Burciu C, D'Souza KM, Raravikar K, Liu J, et al. Exenatide protects against glucoseand lipid-induced endothelial dysfunction: Evidence for direct vasodilation effect of glp-1 receptor agonists in humans. Diabetes 2015; 64(7): 2624-2635.
11. Gurkan E, Tarkun I, Sahin T, Cetinarslan B, Canturk Z. Evaluation of exenatide versus insulin glargine for the impact on endothelial functions and cardiovascular risk markers. Diabetes Res Clin Pract 2014; 106(3): 567-575.

12. Patti AM, Nikolic D, Magan-Fernandez A, Giglio RV, Castellino G, Chianetta R, et al. Exenatide once-weekly improves metabolic parameters, endothelial dysfunction and carotid intima-media thickness in patients with type-2 diabetes: An 8-month prospective study. Diabetes Res Clin Pract 2019; 149: 163-169.
13. Rizzo M, Rizvi AA, Patti AM, Nikolic D, Giglio RV, Castellino G, et al. Liraglutide improves metabolic parameters and carotid intima-media thickness in diabetic patients with the metabolic syndrome: an 18-month prospective study. Cardiovasc Diabetol 2016; 15(1): 162.
14. Gaspari T, Welungoda I, Widdop RE, Simpson RW, Dear AE. The GLP-1 receptor agonist liraglutide inhibits progression of vascular disease via effects on atherogenesis, plaque stability and endothelial function in an ApoE(-/-) mouse model. Diabetes Vasc Dis Res 2013; 10(4): 353-360.
15. Rakipovski G, Rolin B, Nøhr J, Klewe I, Frederiksen KS, Augustin R, et al. The GLP-1 Analogs Liraglutide and Semaglutide Reduce Atherosclerosis in ApoE -/- and LDLr -/- Mice by a Mechanism That Includes Inflammatory Pathways. JACC Basic to Transl Sci 2018; 3(6): 844-857.
16. Arakawa M, Mita T, Azuma K, Ebato C, Goto H, Nomiyama T, et al. Inhibition of monocyte adhesion to endothelial cells and attenuation of atherosclerotic lesion by a glucagon-like peptide-1 receptor agonist, exendin-4. Diabetes 2010; 59(4): 1030-1037.
17. Nagashima M, Watanabe T, Terasaki M, Tomoyasu M, Nohtomi K, Kim-Kaneyama J, et al. Native incretins prevent the development of atherosclerotic lesions in apolipoprotein E knockout mice. Diabetologia 2011; 54(10): 2649-2659.
18. Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. Endocr Pract 2017; 23: 1-87.
19. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019; 394(10193): 121-130.
20. Hernandez AF, Green JB, Janmohamed S, D'Agostino RB, Granger CB, Jones NP, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet (London, England) 2018 ;392(10157):1519-1529.
21. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med 2016; 375(19): 1834-1844.
22. Drucker DJ. The Ascending GLP-1 Road From Clinical Safety to Reduction of Cardiovascular Complications. Diabetes 2018; 67(9): 1710-1719.
23. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2017; 377(13): 1228-1239.
24. Koska J, Migrino RQ, Chan KC, Cooper-Cox K, Reaven PD. The Effect of Exenatide Once Weekly on Carotid Atherosclerosis in Individuals With Type 2 Diabetes: An 18-Month Randomized Placebo-Controlled Study. Diabetes Care 2021; 44(6): 1385-1392.
25. Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol 2002; 39(2): 257-265.
26. Cai JM, Hatsukami TS, Ferguson MS, Small R, Polissar NL, Yuan C. Classification of human carotid atherosclerotic lesions with in vivo multicontrast magnetic resonance imaging. Circulation 2002; 106(11): 1368-1373.
27. Zhang Y, Guallar E, Malhotra S, Astor BC, Polak JF, Qiao Y, et al. Carotid Artery Wall Thickness and Incident Cardiovascular Events: A Comparison between US and MRI in the Multi-Ethnic Study of Atherosclerosis (MESA). Radiology 2018; 289(3): 649-657.
28. Akbas EM, Timuroglu A, Ozcicek A, Ozcicek F, Demirtas L, Gungor A, et al. Association of uric acid, atherogenic index of plasma and albuminuria in diabetes

mellitus. Int J Clin Exp Med 2014; 7(12): 5737.
29. Tonneijck L, Muskiet MHA, Smits MM, Bjornstad P, Kramer MHH, Diamant M, et al. Effect of immediate and prolonged GLP-1 receptor agonist administration on uric acid and kidney clearance: Post-hoc analyses of four clinical trials. Diabetes Obes Metab 2018; 20(5): 1235-1245.