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Original Article *Özgün Araştırma*

THE EFFECTS OF EXENATIDE TREATMENT ON METABOLIC PARAMETERS, GHRELIN, GDF-15 AND FGF-21 IN OBESE TYPE 2 DIABETIC PATIENTS

Obez Tip 2 Diyabetik Hastalarda Eksenatid Tedavisinin Metabolik Parametreler, Ghrelin, GDF-15 ve FGF-21 Üzerine Etkileri

Müge ÖZSAN YILMAZ[1], Oğuzhan ÖZCAN[2]

[1]*Hatay Mustafa Kemal University, Faculty of Medicine, Department of Endocrinology and Metabolism, HATAY, TÜRKİYE*
[2]*Hatay Mustafa Kemal University, Faculty of Medicine, Department of Medical Biochemistry, HATAY, TÜRKİYE*

ABSTRACT

Objective: Exenatide and similar drugs which have Glucagon Like Peptide-1(GLP-1) like effects have been used frequently in the treatment of diabetes and obesity in recent years. In this study we aimed to investigate the effects of exenatide on ghrelin, FGF-21 and GDF-15 which are known to be associated with appetite and metabolic disorders.

Material and Methods: Thirty patients with Type 2 Diabetes Mellitus with a Body Mass Index of 35 kg/m^2 and above who are still ongoing treatment for diabetes but not on target (HbA1c>7%) and exenatide treatment was started were included in the study. Venous blood samples were collected for the measurements of complete blood count, biochemical parameters, HbA1c, ghrelin, FGF-21, GDF-15. After 3 months of treatment initial evaluations and biochemical tests were repeated.

Results: Mean age of the patients was 50.43±10.35 years. Twenty-one (70%) were female and 9 (30%) were male. Mean Hb A1c of the patients was 9.68±2.02%. After 3 months of exenatide treatment a significant decrease in body weight and body mass index was observed (p<0.001). There was also significant decrease in Ghrelin and GDF-15 levels (p<0.001).

Conclusion: Our study is the first study in which these three markers were evaluated together in obese type 2 diabetics. It is thought to be that Ghrelin, FGF-21 and GDF-15 are play role in obesity and type 2 diabetes mellitus pathogenesis together in different ways.

***Keywords**: Obesity, exenatide, ghrelin, Fibroblast Growth Factor 21, Growth Differentiation Factor 15*

ÖZ

Amaç: Glukagon Benzeri Peptid-1(GLP-1) benzeri etkileri olan eksenatid ve benzeri ilaçlar son yıllarda diyabet ve obezite tedavisinde sıklıkla kullanılmaktadır. Bu çalışmada eksenatidin iştah ve metabolik bozukluklarla ilişkili olduğu bilinen hormonal özellikli peptidler olan ghrelin, FGF-21 ve GDF-15 üzerine etkilerini araştırmayı amaçladık.

Gereç ve Yöntemler: Tip 2 Diabetes Mellitus'lu, Vücut Kitle İndeksi 35 kg/m^2 ve üzerinde olan, diyabet tedavisi devam eden ancak hedefte olmayan (Hb A1c>%7) ve eksenatid tedavisi başlanan 30 hasta çalışmaya dahil edildi. Tam kan sayımı, biyokimyasal parametreler, HbA1c, ghrelin, FGF-21, GDF-15 ölçümleri için venöz kan örnekleri alındı. 3 aylık tedaviden sonra ilk değerlendirmeler ve biyokimyasal testler tekrarlandı.

Bulgular: Hastaların yaş ortalaması 50.43±10.35 yıl olup; 21'i (%70) kadın, 9'u (%30) erkekti. Hastaların ortalama Hb A1c'si %9.68±2.02 idi. Eksenatid tedavisinden sonra vücut ağırlığında ve vücut kitle indeksinde önemli bir azalma gözlendi (p<0.001). Ghrelin ve GDF-15 düzeylerinde de anlamlı düşüş vardı (p<0.001).

Sonuç: Çalışmamız, obez tip 2 diyabetlilerde bu üç belirtecin birlikte değerlendirildiği ilk çalışmadır. Ghrelin, FGF-21 ve GDF-15'in obezite ve tip 2 diabetes mellitus patogenezinde birlikte farklı şekillerde rol oynadığı düşünülmektedir.

***Anahtar Kelimeler**: Obezite, eksenatid, ghrelin, Fibroblast Büyüme Faktörü 21, Büyüme Farklılaşma Faktörü 15*

Correspondence / Yazışma Adresi: **Dr. Müge ÖZSAN YILMAZ**
Hatay Mustafa Kemal University, Faculty of Medicine, Dept. of Endocrinology and Metabolism, HATAY, TÜRKİYE
Phone / Tel: +90 532 5913735 **E-mail /** E-posta: mugeozsan@gmail.com
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INTRODUCTION

Obesity is an important health problem which is increasing in our country and quite common in especially type 2 diabetics. There are many common mechanisms in the pathophysiology of diabetes and obesity and their association is almost inevitable. Gastrointestinal system is a part of the endocrine system and secretes many regulatory peptides. One of them, Glucagon-like peptide-1 (GLP-1) is both a gastrointestinal hormone and neuropeptide. GLP-1 is primarily glucose-dependent insulin stimulating hormone and also suppresses food intake via central nervous system (1,2). Exenatide and similar drugs which have GLP-like effects have been used frequently in the treatment of diabetes in recent years. Exenatide requires two injections a day and is more effective in lowering postprandial glycemia and provides an average weight loss of 2-4 kilograms unlike other anti-hyperglycemic drugs and insulin (3). It has been shown that exenatide lowers ghrelin and FGF21 levels in a small number of studies conducted in type 2 diabetic patients but there is no study in the literature regarding the effect of GDF-15 which is considered to be as another metabolic regulator (4,5).

Ghrelin is a peptide with 28 amino acids and is a growth hormone-releasing receptor-1a (GHS-R1a) isoform isolated from the stomachs of humans and rats (6). Ghrelin's stimulating effect on growth hormone (GH) release increases nutrition and weight gain by regulating energy balance (7). Ghrelin also plays a role in glucose metabolism by reducing insulin secretion and sensitivity (8). It negatively affects diabetes regulation due to its effects on both insulin and food intake.

The fibroblast growth factor family (FGFs) is a large gene family involved in cell growth and differentiation, embryonic development, angiogenesis and wound healing. Fibroblast growth factor-21 (FGF-21), a member of this family, is a protein with hormonal effects that regulates fatty acid and glucose metabolism (9). FGF-21 levels have been found increased in abdominal obesity, insulin resistance, type 2 DM, hepatosteatosis, and hypertriglyceridemia (10).

GDF-15 which is previously known as macrophage inhibitory cytokine-1 is a member of the transforming growth factor beta (TGF-β) family (11). Although it can be found widely in many cells and tissues the main sources of GDF-15 in diabetic patients are macrophages, white adipose tissue and liver cells. Biomechanical stress, ischemia, anoxia, angiotensin II, macrophage colony stimulating factor, TGF-β and inflammatory cytokines (tumor necrosis factor alpha, interleukins (IL-2, IL-4, IL-6) trigger GDF-15 production (12). In studies conducted with type 2 diabetics serum GDF-15 levels have been shown to be positively associated with BMI, HbA1c, insulin resistance, hip height ratio, body fat, age, arterial blood pressure, triglyceride, creatinine, glucose, hs-CRP, diabetic nephropathy, and negatively associated with insulin and anemia (13,14).

In this study our aim is to investigate the effect of exenatide treatment in obese type 2 diabetic patients on metabolic parameters and the levels of FGF-21 and GDF-15, which are considered as metabolic markers of ghrelin which has a role on impaired food intake and weight balance.

MATERIALS AND METHODS

Thirty patients with Type 2 Diabetes Mellitus who applied to our Endocrinology and Metabolism Department with a BMI of 35 kg/m^2 and above, who are still under ongoing treatment for diabetes but have not reached the target (HbA1c> 7%) and for whom exenatide treatment was started included in the study. Patients with pancreatitis, cardiovascular, gastrointestinal, hepatic, renal, rheumatologic, oncological, infectious diseases and patients with other endocrine diseases other than hyperlipidemia and hypertension, using any GLP mimetic, DPP4 inhibitor, SGLT2 inhibitor were excluded from the study. Written informed consent was obtained from the patients who were included in the study in accordance with the terms

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of the Helsinki declaration on ethical issues. Ethics Committee Approval was obtained from Hatay Mustafa Kemal University Tayfur Ata Sökmen Medicine Faculty Ethics Committe of Clinical Research at 27.10.2016 with decision number 180.

Lifestyle changes including diet and physical exercise were suggested to the patients in line with American Diabetes Association (ADA) recommendations (15). The patients were seen in the outpatient clinic after 12 hours of fasting. Demographic data of the patients such as age and gender were recorded, and height and body weight measurements were done. Body mass indexes were calculated using the formula BMI = Body weight/Height^2 (kg/m^2). Blood pressure measurements of the patients were performed. Venous blood samples were collected to study the measurements of complete blood count, biochemical parameters, Hb A1c, ghrelin, FGF-21, GDF-15. Exenatide treatment was started as 2×5 mcg subcutaneously and increased to 2×10 mcg after the 1st month. Patients were evaluated in terms of treatment compliance and side effects every month. After 3 months of treatment initial evaluations and biochemical tests were repeated.

Biochemical Analysis

Morning fasting blood samples from the patients were taken into biochemistry tubes and whole blood samples were taken into tubes containing EDTA as anticoagulant. Hb A1c tests were analyzed by chromatography (BIO-RAD, Variant II, USA) in the routine biochemistry laboratory on the same day and the results were recorded. The blood taken into the biochemistry tube was centrifuged at 1500 rpm for 10 minutes and the serums were portioned and stored at -80 degrees until the working day. Among routine parameters, serum glucose, creatinine, potassium, AST, ALT, alkaline phosphatase, amylase, lipase, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, TSH levels were measured spectrophotometrically with an autoanalyzer in the routine biochemistry laboratory (Siemens Advia 1800, Germany) on the same day and the results were recorded. Serum FGF-21, GDF-15 and Ghrelin levels were studied by ELISA method using commercial kits (Thermo Scientific Multiscan Go-Finland). Performance data of the kits used are as follows:

Analytical range for Human GDF-15 kit is 70-4480 pg/mL, Intra-Assay precision=6.3%, Inter-Assay precision=6.9%.

Analytical range for Human FGF-21 kit is 60-960 pg/mL, Intra-Assay precision<10%, Inter-Assay precision>12%

Analytical range for Human Ghrelin kit is 80-3000 pg/mL, Intra-Assay precision=10%, Inter-Assay precision=12%.

Statistical Analyses

The data were analyzed using SPSS for Windows, version 21.0. Data were shown as mean ± standard deviation (±SD). In numerical data without normal distribution, median was used. *P* value of less than 0.05 was considered statistically significant. Individual variables were compared by paired *t* test for normally distributed variables and Wilcoxon signed rank test for non-normal variables. Pearson correlation analysis was used to investigate the association between serum ghrelin and the other laboratory parameters.

RESULTS

Thirty type 2 diabetic patients were included in the study. Mean age of the patients was 50.43±10.35 years. Twenty-one (70%) were female and 9(30%) were male. Mean duration of diabetes of the patients was 7.65±1.21 years. While no diabetes complication was observed in 50% (n=15) of the patients, 40% (n=12) had at least one complication and 10% (n=3) had multiple complications. Sixteen patients (53.3%) were using metformin alone or in combination with another oral antidiabetic, while 14 patients (46.6%) were using metformin and insulin. The average A1C of the patients was 9.68±2.02% and exenatide treatment was added to their current treatment. Clinical and biochemical data of

the patients at baseline and third month are shown in Table 1.

In the third month of exenatide treatment a significant decrease in body weight and associated body mass index was observed ($p<0.001$). A significant decrease was observed in A1c, AST, ALT levels of the patients but no increase was found in amylase and lipase values (Table 1). While there was a significant decrease in serum Ghrelin and GDF-15 levels there was no change in FGF-21 (Table 2, Figure 1).

Table 1. Clinical and laboratory findings of patients at the beginning and 3rd month of the exenatide therapy

	Baseline	**3rd month**	***p***
Body weight (kg)	113.5 ±15.1	109.6±15.6	**<0.001**
Body mass index (kg/m^2)	42.6 ± 5.3	41.3 ± 5.5	**<0.001**
Hemoglobin (g/dL)	12.9±1.5	12.9±1.3	0.753
WBC (10^3/μL)	8.7 ± 2.5	8.1±1.6	0.974
Platelet (10^3/μL)	263.3 ± 64.7	276.9 ± 71.1	0.558
Fasting blood glucose (mg/dL)	180.3 ± 76.4	163.8 ± 74.7	0.548
A1c (%)	9.68± 2.02	7.96±1.92	**<0.001**
Creatinine (mg/dL)	0.76±0.15	0.75±0.13	0.624
Potassium (mmol/L)	4.43±0.40	4.37±0.42	0.410
AST (U/L)	30.20±15.81	18.83±4.87	**<0.001**
ALT (U/L)	32.56±18.37	22.40±9.95	**<0.001**
Alkaline phosphatase (U/L)	58.44±30.91	50.43±28.92	0.202
Amylase (U/L)	35.62±12.91	25.52±16.40	0.982
Lipase (U/L)	26.23±14.69	26.52±16.40	0.542
Total cholesterol (mg/dL)	208.74±53.32	193.80±54.94	0.139
HDL cholesterol (mg/dL)	36.06±7.66	39.56±9.73	**0.007**
LDL cholesterol (mg/dL)	121.60±44.79	113.61±45.50	0.600
Triglyceride (mg/dL)	242.98±131.61	194.38±98.10	**0.010**
TSH (μIU/mL)	1.45±0.55	1,58±0.83	0.943

Table 2. Serum Ghrelin, GDF-15, FGF -21 levels of patients at the beginning and 3rd month of the exenatide therapy

	Baseline				**3rd month**				**p**
	Mean	Median	Min	Max	Mean	Median	Min	Max	
Ghrelin	759.24	544.80	80.00	2896.00	431.88	329.45	80.00	2619.70	**0.01**
GDF-15	273.39	230.75	70.30	648.70	164.74	140.30	58.30	499.30	**0.01**
FGF-21	229.33	130.80	60.00	960.00	242.34	147.60	70.30	1212.00	0.83

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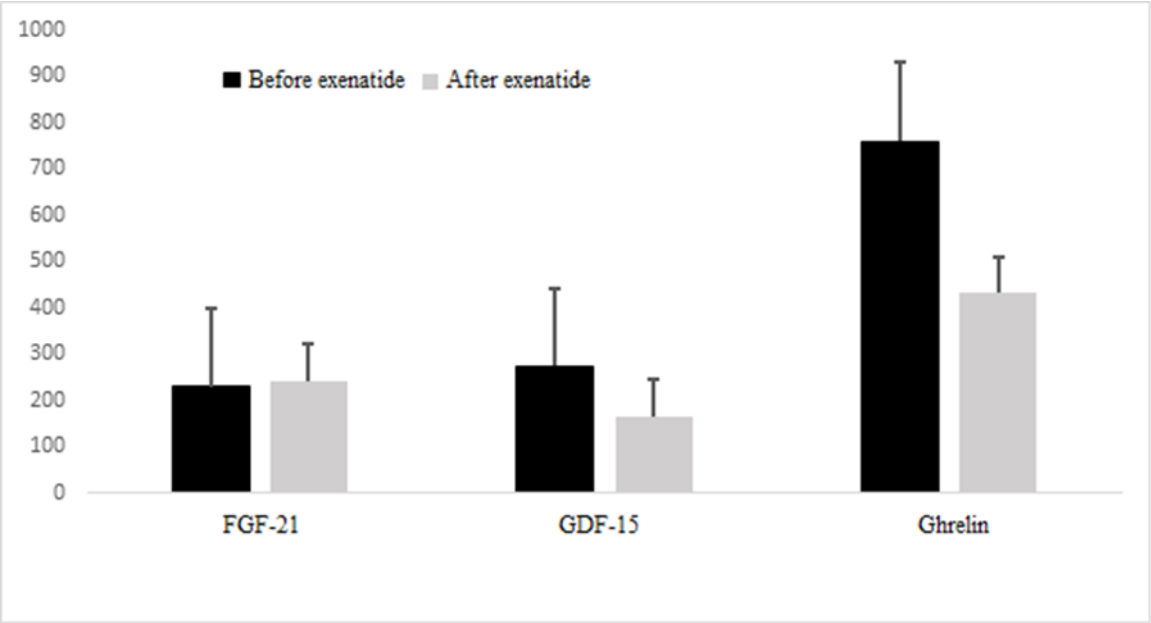

Figure 1: Changes in Ghrelin, GDF-15 and FGF-21 levels after exenatide treatment

DISCUSSION

It is well known that the effects of intestinal peptides on food intake, nutritional status, and growth are related to glucose metabolism and insulin resistance. Drugs that are effective on intestinal peptides especially GLP-1 have been preferred in the treatment of diabetes in recent years due to their early and long-term positive effects. Weight loss effects, cardiovascular positive effects with some members of these group and not causing hypoglycemia have increased the use of these drugs.

In patients with T2DM, exenatide slowed gastric emptying; reduced fasting hyperglycemia and hyperglucagonemia; stimulated glucose-dependent insulin secretion; attenuated postprandial excursions of glucose, insulin, and glucagon; inhibited food intake and reduced body weight (16). Studies were reported on which molecular mechanisms play a role for these positive effects and it seems the studies will continue to be done. The subject of our study essentially arose from here. Thus, we investigated how ghrelin and GDF-15 and FGF-21 levels, whose metabolic effects have been studied in various subjects and type 2 diabetics, change with exenatide treatment and whether they play a role in the effects of exenatide.

When a peptide hormone ghrelin binds to its receptor, hunger is stimulated and growth hormone secretion increases. Ghrelin thus appears as the main determinant in energy balance (6). Although ghrelin is mostly expressed in the stomach, there are ghrelin-producing cells in pancreatic islets. Insulin and glucagon release is also regulated through these cells. Ghrelin antagonism is seen as a new approach in the treatment of type 2 diabetes by increasing insulin secretion and peripheral insulin effect (17). There are several animal studies examining the effects of exenatide on ghrelin. In one of the limited studies examining the effect of exenatide use on ghrelin in type 2 diabetics, a decrease was found in ghrelin levels measured after 3 months of exenatide therapy similar to our study (4). Other studies generally reported the acute effects on ghrelin.

The decreased levels of ghrelin in our patients after treatment and the changes in A1c, body weight and BMI prove that exenatide is also effective over ghrelin. Ghrelin levels are negatively correlated with BMI and insulin resistance. Glucose and insulin play an important

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role in the suppression of postprandial ghrelin. Ghrelin secretion is impaired in obesity and insulin resistance interestingly. There is decreased mean fasting ghrelin level in obese patients and blindness in postprandial suppression (18). Ghrelin is also closely related to lipid metabolism (19). In our patients a significant increase in HDL levels and a significant decrease in triglycerides were observed. This finding can be explained by the better blood glucose regulation of the patients and it may be thought that the decrease in ghrelin that occurs with exenatide treatment may have contributed to this positive effect.

FGF-21, a member of the fibroblast growth factor family and secreted by the liver, has glucose-lowering effects in type 2 diabetic patients independent of insulin. It achieves this effect by increasing the use of glucose by peripheral tissues and by suppressing gluconeogenesis in the liver and by improving insulin resistance (20,21). In some human and animal studies conducted in type 2 diabetes, it has been shown that plasma FGF21 levels increase but its biological activity decreases (22,23). Additionally, it has also been shown that FGF-21 levels increase in metabolic disorders such as abdominal obesity, insulin resistance, type 2 DM, hepatosteatosis, and hypertriglyceridemia (10).

In a study similar to our study, newly diagnosed type 2 diabetics were given exenatide for 12 weeks and FGF21 and insulin levels were examined. First of all, FGF21 levels in these patients were found to be higher than healthy controls. FGF21 decreased after exenatide treatment, and this was found to be correlated with fasting insulin and FGF21 levels (5). In our study although 3-month exenatide treatment had positive effects on weight control, A1c, HDL and triglyceride we did not find a significant change in the FGF21 levels of the patients. However, compared to this study, the BMI of the patients in our study were quite high (31.4±4.8 vs 41.3±5.5). While it has been shown in previous studies that FGF21 has a positive correlation with the degree of obesity, another study has shown that FGF21 provides weight loss by activating brown fat cells in white adipose tissue (24,25). Obesity is a condition in which FGF21 resistance is observed (26). The morbid obesity of our patients may be a reason for the lack of change in FGF21, which is associated with the degree of obesity.

GDF-15, a member of the transforming growth factor beta (TGF-β) family and can be found in many tissues, is a stress-induced cytokine (11). It has been shown in various studies that its level increases in obese patients and is also important in determining risk in cardiovascular diseases (27,28). GDF-15 levels in type 2 diabetics have been shown to correlate with fasting glucose levels, A1c, insulin resistance, BMI, fat ratio, hip height ratio, triglyceride levels, CRP, creatinine, arterial blood pressure, and diabetic nephropathy (12,13) Before treatment in our patients, high levels of GDF-15 decreased with the decrease of BMI and favorable metabolic changes such as A1c reduction. According to our current knowledge, there is no study in the literature examining the effect of exenatide treatment on GDF-15. This decrease may be due to the direct effect of exenatide as well as weight reduction and A1c improvement with treatment.

Studies have shown that GDF-15 can be used as an inflammation marker like CRP in various diseases. As in our study, the decrease in GDF-15 that occurs with exenatide may cause suppression of inflammatory processes in diabetic patients and thus decrease of various comorbidities that may occur. In the XENDOS study this effect came to the fore when it was revealed that the occurrence of insulin resistance and diabetes in the following years in obese individuals is associated with GDF-15 (13). Also, GDF-15 has been shown to be important in determining the diabetes risk especially in the population under 60 years of age in Malmö Diet and Cancer-Cardiovascular Cohort study (29). In addition, it has been shown that increased GDF-15 levels are associated with an increased incidence of malignancy in type 2 diabetic patients (30).

In conclusion, this is the first study in which these three markers that have been shown to play role both in the pathogenesis and complications of type 2 diabetes and obesity were evaluated together. The significant decrease we achieved with ghrelin and GDF-15 with exenatide treatment was together with the positive results of the treatment. We did not detect a change in FGF-21 but this suggests that our patients may have a possible FGF-21 resistance.

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