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The effect of serum activated ghrelin hormone on glycemic control in the diabetic patients with excessive body mass index

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ABSTRACT

Objective: In the literature, plasma ghrelin level was found to be lower in patients with obesity or diabetes in a few studies. However, there is no study comparing ghrelin level in non-diabetic and diabetic patients with overweight or obesity. We have two aims in this study; first to show whether plasma ghrelin levels in type 2 diabetes mellitus patients with excessive body mass index (BMI) decrease the level of a cumulative ghrelin which we expect in both diabetes-related and obesity-related conditions, secondly to study whether there is a correlation between ghrelin level and diabetes complications.

Patients and Methods: Ethics committee decision and written informed consent from patients were received before the study. 57 BMI≥25 type 2 diabetic patients treated and followed up in the diabetic outpatient clinic and 25 BMI≥25 subjects without diabetes mellitus (control group) were included in this case-control study. Pregnant women, patients with malignancy and under 18 years old were excluded. The results were evaluated by the SPSS statistical program.

Results: The ghrelin and BMI values of the diabetic patients with excessive BMI and the non-diabetic patients with excessive BMI were not statistically different. No statistical significant correlation between ghrelin and haemoglobin A1c (HbA1C), BMI, retinopathy, neuropathy, albuminuria, and macrovascular complications was found in the type 2 diabetic patients with overweight or obesity.

Conclusion: The presence of diabetes in addition to patients with excessive BMI does not cause ghrelin levels to decrease more than expected.

Keywords: Ghrelin, Diabetes mellitus, Obesity, Overweight

1. INTRODUCTION

Ghrelin was discovered in 1999 as a growth hormone releasing peptide [1]. It is released mainly by the gastric cells. Ghrelin hormone increases appetite, stimulates eating and gastric motility, but is also adipogenic [2-8]. Its blood level increases in fasting and hypoglycaemia conditions [9]. Intracerebroventricular ghrelin administration increases nitric oxide synthesis (NOS) levels in the hypothalamus. It is observed that ghrelin's effect on increasing food intake is inhibited by the administration of N-nitro-L-arginine methyl ester [10]. It has opposite effects than the effects of leptin and obestatin in the body [11].

Plasma ghrelin level is inversely proportional to body mass index (BMI) in non-diabetic patients with excessive BMI and type 2 diabetes mellitus patients [12,13].

Our objective in this study is to show whether plasma ghrelin levels in type 2 diabetes mellitus patients with excessive BMI decrease the level of a cumulative ghrelin that we expect in both diabetes-related and obesity-related conditions.

2. PATIENTS and METHOD

Fifty-seven BMI≥25 type2 diabetic patients treated and followed up in the diabetic outpatient clinic and 25 BMI≥25 subjects without diabetes mellitus (control group) were included in the study. Ethics committee approval (Ministry of Health Okmeydanı Education and Training Hospital's Ethics committee, 23-12-2008, number:156) and written informed consent from patients were received before the study. Before the

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start of the study, disease duration, age, sex, BMI, height, weight, waist, hip measurements, concomitant diseases were recorded in all patients.

Serum samples were obtained from patients for fasting blood glucose, HbA1C, urea, creatinine, total cholesterol, triglycerides, LDL-cholesterol, HDL-cholesterol, VLDL-cholesterol, activated ghrelin measurements.

Activated ghrelin was measured by using Linco Research's Human Ghrelin (activated) (Linco Research, Missouri, USA) Elisa Kit, sandwich ELISA method. The samples taken into the dry tube were centrifuged within half an hour, the plasma was separated and the samples were frozen and stored. After all patient and control serums were collected, samples were analysed in accordance with the stages of kit prospectus.

The BMI of the patients was calculated with the formula weight (kg) / height^2 (meters).

Haemoglobin A1c: was measured by high performance liquid chromatography (HPLC) method on the Bio DPC Adams A1c device (Arkray Inc., Kyoto, Japan). Normal reference intervals were 4.6-5.2%.

Glucose and urea: were studied by photometric method in the Olympus AU2700 autoanalyzer (Beckman Coulter Inc, CA, USA).

Total cholesterol, triglyceride, HDL, LDL, VLDL-cholesterol: were studied by photometric method in the Roche modular V2 autoanalyzer.

Statistical Analysis

Statistical analysis was performed in two stages. The first stage is for patient group data and the second stage is for the analysis of both the patient and the control group integrated data set. The patient group consisted of a total of 57 diabetic patients with excessive BMI, while the non-diabetic patients with excessive BMI group consisted of 25 subjects. Firstly, the Jarque-Bera test was applied to test the normal distribution of the data. Since, the test result was $p<0.05$, the H1 hypothesis suggesting abnormal distribution was accepted. Thus, it was considered that non-parametric methods should be used in the analysis. SPSS (24 version) statistical program was used to analyse data. Kendall's Tau-b, Mann-Whitney U and Wilcoxon W tests were done.

3. RESULTS

The diabetic patients with excessive BMI included in the study were 17 males, 40 females, and the control group consisted of 9 males and 16 females. The mean age of the patient group was 56, mean BMI was 31.1, mean HbA1c was 7.65 and mean ghrelin was 69.5. The mean age of the control group consisting of patients with excessive BMI without diabetes was 53, mean BMI was 32.2, mean HbA1c was 5.4 and mean ghrelin was 70.4. The values of the diabetic patients with excessive BMI index group and the control group consisting of patients with excessive BMI without diabetes are summarized in Table I.

Table I. *Comparison of the values the diabetic patients with excessive body mass index and the control group consisting of patients with excessive body mass index without diabetes*

Patients with excessive body mass index	Diabetic (n=57)	Non-Diabetic (n=25)	P value
	Mean (SD)	Mean (SD)	
Age (years)	56.14 (10.73)	53.04 (10.94)	0.781
BMI (kg/m2)	31.18 (3.81)	32.28 (3.37)	0.703
HbA1c(%)	7.65 (1.49)	5.46 (0.33)	0.001
Ghrelin (pg/mL)	69.59 (9.99)	70.45 (13.89)	0.080
Height (cm)	160.60 (7.93)	165.32 (7.45)	0.956
Weight (kg)	81.29 (12.92)	88.84 (9.88)	0.112
Waist (cm)	103.84 (10.43)	105.68 (8.22)	0.465
Total Chol (mg/dl)	192.11 (43.09)	200.6 (30.73)	0.184
TG (mg/dl)	170.84 (107.8)	162.96 (126.23)	0.839
HDL Chol (mg/dl)	47.61 (12.29)	48.6 (9.22)	0.107
LDL Chol (mg/dl)	111.2 (33.85)	119.84 (27.14)	0.275
VLDL Chol (mg/dl)	34.21(21.62)	32.68 (25.26)	0.813
FBG (mg/dl)	158 (55.84)	91.88 (8.72)	0.001
Urea (mg/dl)	32.61(10.26)	26.92 (8.62)	0.486
Creatinin (mg/dl)	1.04 (0.45)	0.8 (0.16)	0.140

BMI: Body mass index, HbA1c: Hemoglobin A1c, TG: Triglyceride, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: very low-density-lipoprotein, FBG: Fasting blood glucose,

The ghrelin and BMI values of the diabetic patients with excessive BMI group and the patients with excessive BMI group were not statistically different ($p>0.05$).

Ghrelin and HbA1c, BMI, retinopathy, neuropathy, microalbuminuria, and macrovascular complications were compared in diabetic patients with excessive BMI. No statistical significant relationship was found between ghrelin and HbA1C, BMI, retinopathy, neuropathy, albuminuria, and macrovascular complications in the group consisting of obese type 2 diabetic patients ($p>0.05$). The results are summarized in Table II.

Table II. *Corelation between Ghrelin level and metabolic parameters and complications in diabetic patients with excessive body mass index*

Ghrelin	n	P value
HbA1C	57	0.520
BMI	57	0.671
Retinopathy	24	0.929
Neuropathy	11	0.503
Microalbuminuria	28	0.084
Macrovascular complications	19	0.696

HbA1c: Hemoglobin A1c, BMI: Body mass index

4. DISCUSSION

Although, there is no study in diabetic patients with obesity, a few studies about blood ghrelin levels in patients with obesity or diabetes are available in the literature; Shiiya et al., showed in their study that plasma ghrelin levels decrease as BMI increases

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[14]. On the contrary, Verdesh et al., showed in their study that there is a positive correlation between weight and ghrelin [15]. Katsuki et al., showed in their other study that plasma ghrelin levels inversely decreased in type 2 diabetics with abdominal obesity, plasma insulin levels and insulin resistance [16].

The euglycemic clamp study in normal subjects and type 1 DM patients on intensive insulin treatment showed that hyperinsulinemia suppressed plasma ghrelin secretion [17,18]. It was observed that plasma ghrelin concentration increased before meals and decreased rapidly after meals and after intravenous glucose infusion. These studies showed that ghrelin secretion is suppressed in short-term hyperglycemia or hyperinsulinemia.

In a study performed by Ueno et al., the relationship of plasma ghrelin concentration with glycemic control in diabetic patients was studied. 56 male and 52 female patients, 11 of them with type1 diabetes, 97 with type 2 diabetes were included in this study. The selected patients were low-weighted, normal-weighted and obese. The study showed that plasma ghrelin level is inversely proportional to HbA1c. This study showed that poor glycemic control decreased ghrelin levels. However, it could not be observed whether plasma ghrelin level decreases due to poor glycemic control, or decreased ghrelin impairs blood sugar regulation. As known, hyperinsulinemia and obesity decrease plasma ghrelin levels. In this study, patients with obesity and patients without obesity were evaluated in the same group. Since, ghrelin level is affected by BMI, in this study it could not be observed whether plasma ghrelin level decreases due to poor glycemic control, or due to BMI level [19].

Unlike other previous studies, for the first time, blood ghrelin levels were compared in diabetic and non-diabetic patients with excessive BMI in our study. Plasma ghrelin levels of diabetics and non-diabetic patients with excessive BMI are similar, a cumulative ghrelin decrease induced by both diabetes and obesity could not be detected. This shows us that obesity is the major factor affecting ghrelin levels.

Besides, no statistically significant correlation was found between ghrelin and microalbuminuria, neuropathy, retinopathy and macrovascular complications in the diabetic patients with excessive BMI group in our study. Therefore, ghrelin cannot be associated with diabetic complications. On the other hand one study showed that the ghrelin given exogenously has a protective effect in a degree on renal complications in newborn diabetic rats [20].

There is a limitation in this study that could be addressed in future research, studies with a larger number of patients would achieve better results.

The results of this study showed that there are other factors that affect ghrelin in the obesity condition such as other adipokines including leptin and obestatin, and other unknown mechanisms which may play a major role, therefore, additional studies are needed to clarify this issue.

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Compliance with ethical standards

Ethical Approval: The study protocol was approved by the Ministry of Health Okmeydanı Education and Training Hospital's Ethics committee (23-12-2008, number:156). Written informed consent was received from the patients.

Conflict of Interest: We declare that we have no conflict of interest.

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Authors' Contributions: All listed authors contributed to this study accordingly.

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