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RESEARCH ARTICLE

Relation of Plasma Obestatin Levels with BMI and HOMA-IR in Syrian Obese Patients with Type 2 Diabetes

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Abstract:

Background:

Obestatin is a novel hormone derived from preproghrelin, which was reported to inhibit appetite and gastric motility.

Study Aim:

This study aimed to investigate plasma obestatin levels in obese patients with T2D patients, which had not been studied clearly in last researches.

Methods:

23 normal weight subjects, 35 obese subjects and 31 obese patients with T2D participated in the study, the body mass index was calculated. Fasting glucose and insulin levels were measured and the homeostasis model assessment of insulin resistance (HOMA-IR) was determined. Plasma obestatin levels were measured with enzyme-linked immune sorbent assay (ELISA). The relationship between plasma obestatin levels and biochemical parameters was also analyzed.

Results:

Fasting obestatin was significantly lower in obese patients with T2D, comparing to control subjects (mean=6.35 vs12.38ng/ml) and to the non-patients obese group (mean=6.35 vs 7.76 ng/ml). Obestatin levels correlated significantly and negatively with BMI (R=-0. 451; P=0. 01), basal insulin levels (R=-0.737, P<0.0001) and HOMA-IR (R=-0. 764, P<0.0001) in diabetic patients.

Conclusion:

Our results suggest that obestatin may contribute to body weight regulation, and insulin sensitivity could be affected by obestatin levels.

Keywords: Obestatin, BMI, HOMA-IR, Type 2 diabetes mellitus, Homeostasis, Insulin.

1. INTRODUCTION

Diabetes is a major health problem which its prevalence has been increasing over the last years [1], Type 2 diabetes (T2D) accounts for 90-95% of diabetes cases, and characterized by insulin resistance, and obesity in most patients [2], and obesity in most patients [3], and the aim of the medical treatment is to decrease insulin resistance and increase beta cell insulin production [4].

By using bioinformatics, Zhang *et al.* (2005) identified a 23-amino- acid amidated peptide called obestatin, encoded

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by the same precursor gene of ghrelin [5]. Obestatin was claimed to act as a physiological opponent of ghrelin, inhibiting ghrelin orexigenic action. Therefore whereas ghrelin effects are mainly diabetogenic, obestatin behaves as antidiabetogenic peptide by positively affecting on lipid and glucose metabolism [6]. Obestatin and ghrelin are largely produced throughout the GI tract (like stomach, pancreas and duodenum) with predominant expression in the gastric mucosa [7]. In rats, obestatin is found in the GI tract, within the A-like cells and oxyntic glands of the gastric mucosa. In humans, the majority of obestatin specifically found in the crypts of Lieberkuhn and Brunner's glands, and absence from the colon [8].

Obestatin expression has been demonstrated in other tissues, including pancreas, adipose tissue, testis, liver, lung, thyroid, mammary gland, and skeletal muscle, suggesting autocrine/paracrine effects [9].

Several groups have demonstrated obestatin secretion from rat WAT and adipocytes from both mice and humans [10, 11].

In 2008, obestatin was reported to be secreted by human pancreatic islets and pancreatic beta cell lines, to enhance their viability in response to both serum starvation and cytokines and to inhibit apoptosis [12, 13].

Obestatin promotes the generation of pancreatic islet-like clusters together with increased insulin gene expression during endocrine pancreatic precursor cell selection and differentiation. This seems to happen *via* pathways including fibroblast growth factor receptors, neurogenin 3 and Notch receptors, which suggest its role in development and regeneration of pancreas [14]. Notably, the reported anti-apoptotic effects of obestatin in the pancreas seem to mediate *via* support of islet vascularization [13].

A lot of studies show that obestatin suppress food intake, body weight gain, and jejuna constriction in experiment animals [5], which indicates that obestatin may contribute to the regulation of body weight.

Many researchers have studied obestatin in obese people generally but not in obese diabetes patients, except one study (Lipple *et al.* 2008 [15]). This motivated us to study obestatin levels in obese patients with type 2 diabetes, and investigate the relationship of obestatin levels with insulin resistance and body weight regulation in those patients.

2. MATERIALS AND METHODS

Our study is a prospective cross-sectional study. It was conducted at the endocrine clinic at Al-Moassah University Hospital and Faculty of Pharmacy, Damascus University, Damascus, Syria. Informed consent was given to all participants. Ethical approval obtained from the ethical committee of Damascus University. The study included 89 participants divided into three groups:

Normal weight subjects as Control (23 subjects: 9 males, 14 females), obese patients with T2D (31 subjects:10 males, 21 females), obese subjects (35 subjects: 7 males, 28 females).

The obese patients were admitted for the treatment of obesity and type 2 diabetes, they were not consuming alcohol nor tobacco smoking, and they had not been practicing of physical activity.

Based on the World Health Organization (WHO) body weight classes, subjects were normal weight when BMI ranges from 18.5 to 24.9 kg/m^2, Overweight when BMI ranges from 25 to 29.9 kg/m^2, obese when BMI$\geq$ 30 kg/m^2 [16].

Both control and obese subjects have no family history of T2DM or other diseases.T2D was diagnosed using the FBG (Fasting Blood Glucose) and OGTT (Oral Glucose Tolerance Test) were used [17].

Patients with diabetes complications and those with type 1 diabetes, congestive heart failure, or any major diseases were eliminated. All subjects were of Syrian origin.

Basal blood samples were drawn between 9-10 A.M. after a 12-hour overnight fast. Samples were collected into both EDTA plastic tubes to analyze obestatin in plasma and HbA1c and empty tubes to do other biochemical analysis, then centrifuged at 4000 rpm (1789×g) for 5 minutes at 4ºC to isolate plasma and serum. Biochemical analysis of glucose and HbA1c were performed at Children's Hospital of Damascus within two hours of sampling. Obestatin levels were measured by sandwich ELISA method using a commercial kit (Sun Red, China) and spectro photo microplate reader at Damascus University (Elysisuno - Human, Germany). Glucose was measured by the enzymatic colorimetric method using an automatic analyzer (Hitachi 911, Japan) and commercial assay kits (Audit Diagnostics, Ireland). Insulin levels were measured by ELISA method using a commercial kit (NOVA TEC Immundiagnostica GmbH, Germany).

Statistical analysis was performed using SPSS 20.0 (IBM Inc., USA). All data were expressed as mean ± SD. Data was analyzed using T –Student to compare the results between groups. categorical variables were compared by using chi-square test. Pearson correlation was used to study the correlation between studied parameters. $p<0.05$ was considered significant.

3. RESULTS

The results of studied biochemical parameters were shown in (Table **1**).

Table 1. Demographic characteristics and biochemical parameters of the study population.

	Control Subjects	Obese and Overweight Subjects	Diabetic Subjects
N (male/female)	23(9/14)	35 (7/28)	31(10/21)
Age (years)	39±9	40 ±13**	41± 9 b**b
weight (kg)	63.77±3	83.43±5*	93.19±6*
BMI (kg/m^2)	22.65 ±1.7	32.98 ± 5.06*	35.25 ± 4.33*a
HbA1c (%)	4.9±2.2	5.3±0.77**	7.2±0.8a*a
Insulin (µU / ml)	6.15±0.93	10.82 ± 4.59*	11.1 ± 5.25 b*
Glucose (mg/dl)	95.6±5.5	100 ± 10.5**	191.7± 61.8a *
HOMA-IR	1.45±0.28	2.66 ± 1.15*	5.14 ± 2.45a*
Obestatin (ng/ml)	12.38±3.74	7.76 ± 2.09*	6.35 ± 2.48a*

Data presented as mean ± standard deviation. BMI, body mass index; HOMA-IR, homeostasis model assessment –insulin resistance index. * P<0.05, ** P>0.05 compared with control group. a P<0.05, b P>0.05 compared with obese subjects.

Obestatin levels did not significantly differ from men and women.

Mean ± SD values of obestatin were: 12.38 ± 3.74 ng/ml for control subjects, 7.76 ± 2.09ng/ml for obese subjects. obestatin levels were significantly lower ($p<0.0001$) in obese subjects compared to control subjects.

Mean ± SD values of obestatin were: 6.35 ± 2.48 ng/ml for patients with T2D. Obestatin levels were significantly lower ($p<0.0001$) in patients with T2D compared to control subjects.

Obestatin levels were significantly lower in patients with T2D as compared to obese subjects ($p = 0.014$) (Fig. **1**).

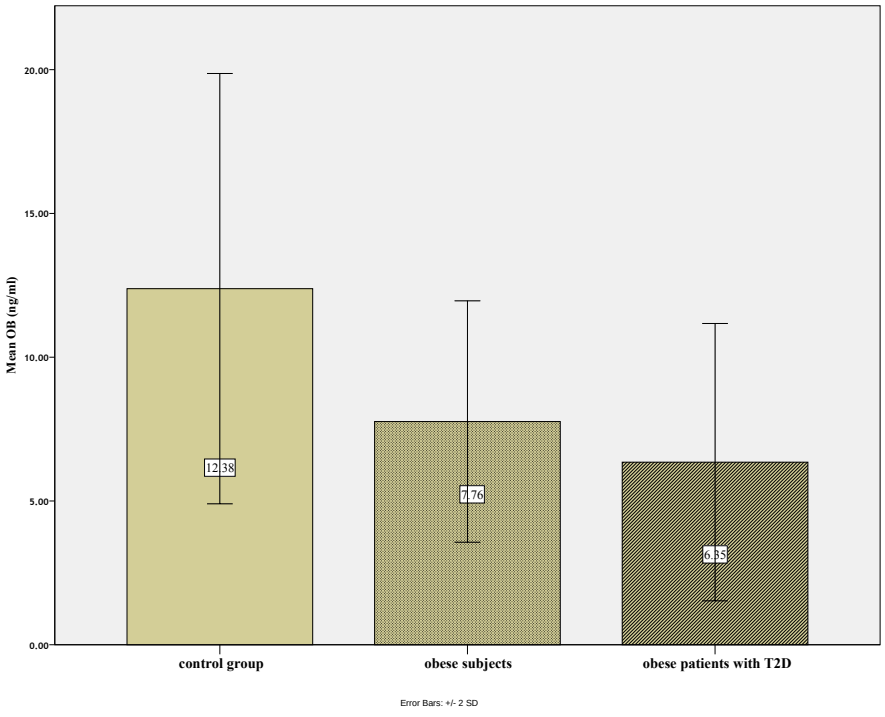

Fig. (1). Plasma obestatin levels in the three groups.

Levels of HOMA-IR (Fig. **2**) and fasting blood glucose (Fig. **3**) were significantly higher (P<0.0001) in diabetic patients as compared to control group and obese subjects, whereas levels of insulin were not significantly (p = 0.817) higher in patients with T2D compared to obese subjects (Fig. **4**).

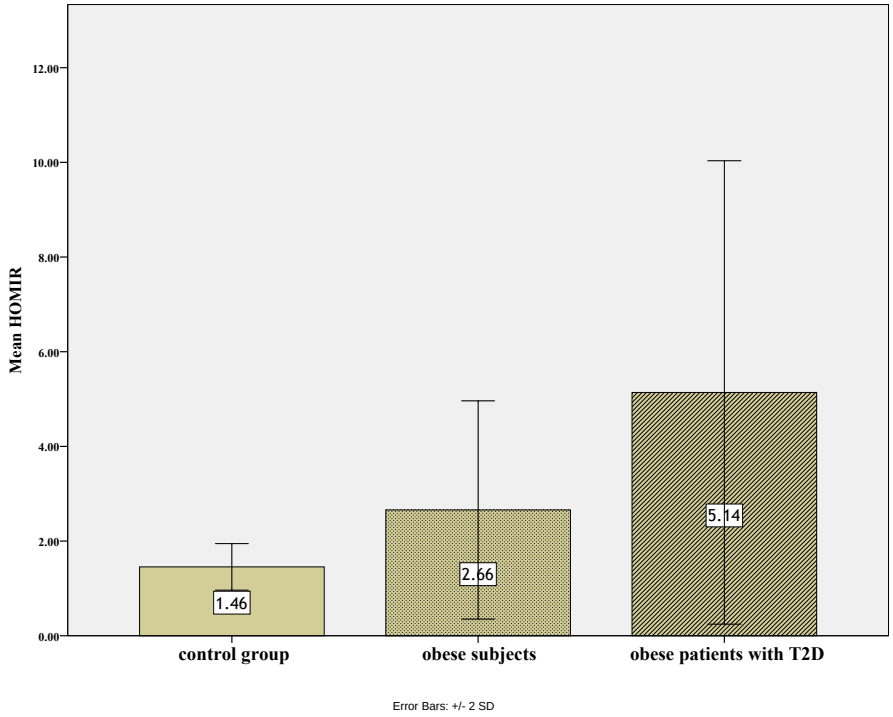

Fig. (2). HOMA-IR in the three groups.

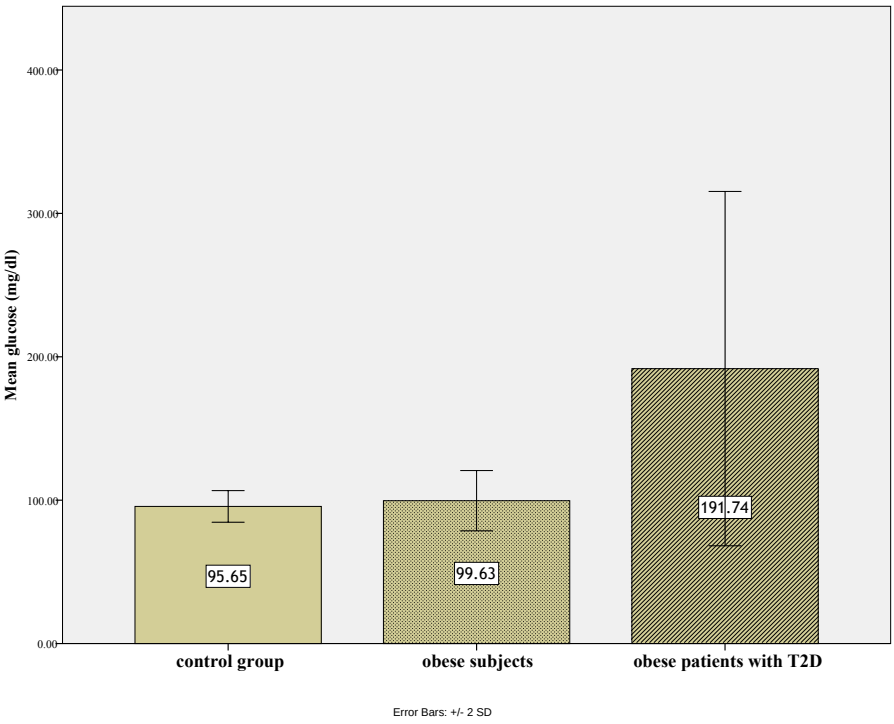

Fig. (3). Glucose levels in the three groups.

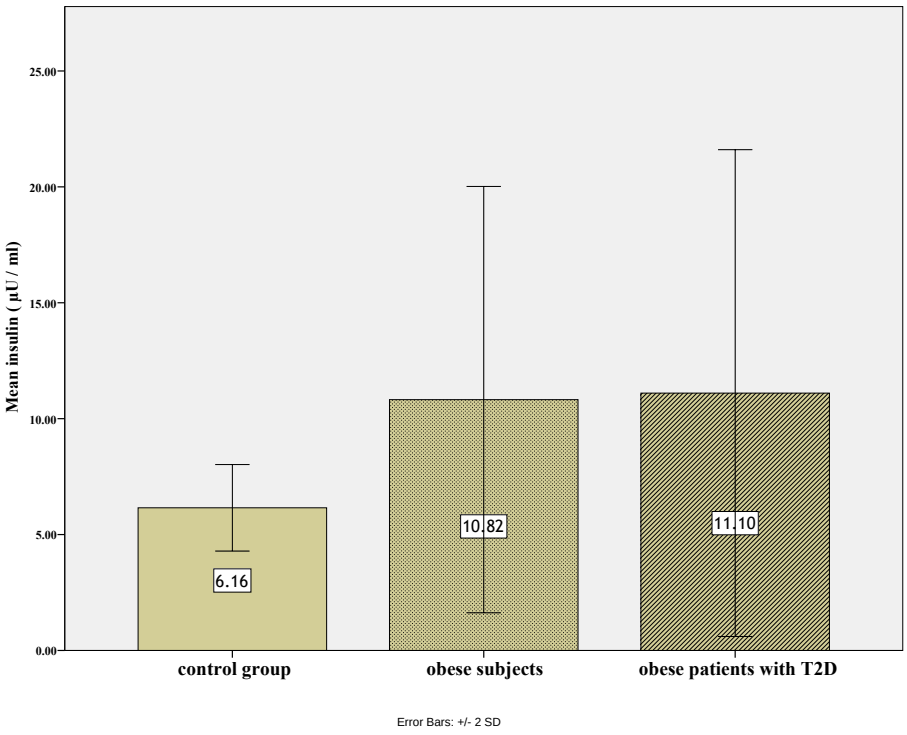

Fig. (4). Insulin levels in the three groups.

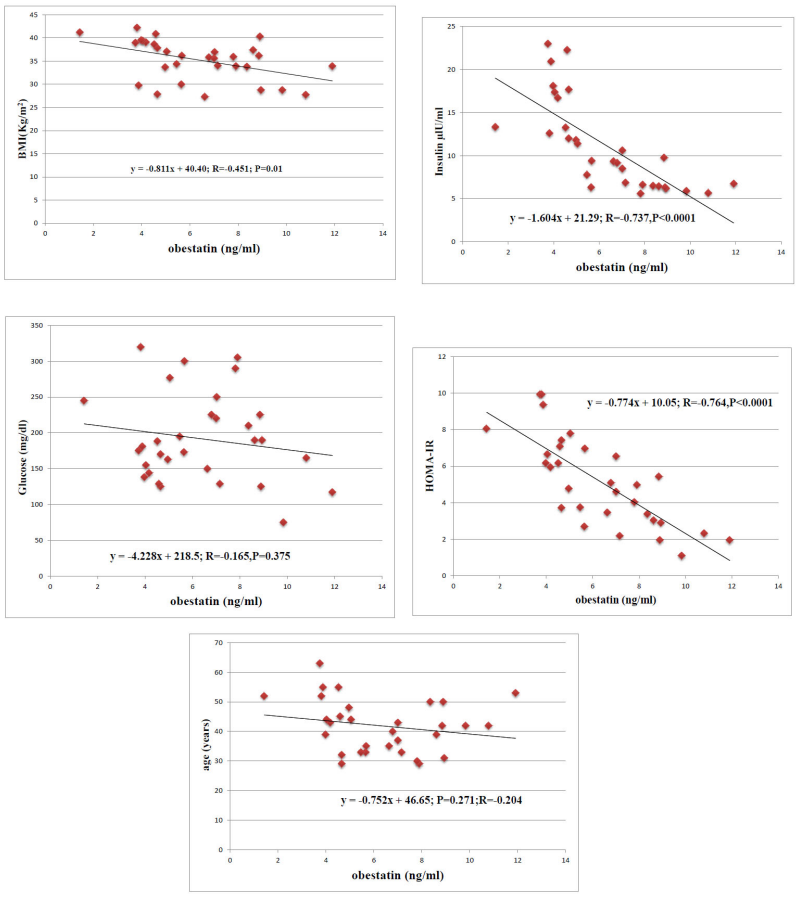

Fig. (5). Correlation between obestatin and BMI, insulin, glucose, HOMA-IR and age.

Levels of obestatin correlated significantly and inversely with BMI values (R = -0. 451; P = 0.01), insulin levels (R = -0. 737, P<0. 0001) and HOMA-IR (R = -0. 764,P<0.0001), but it did not correlate significantly with fasting blood glucose levels (R =- 0. 165, P = 0. 375) nor age (R = -0. 204, P = 0.271) in diabetic patients (Fig. **5**).

4. DISCUSSION

In this study, we measured plasma obestatin levels in patients with type 2 diabetes (T2D) to better understand the role of Obestatin in this disease. Our results showed that Obestatin levels were significantly lower in patients with T2D as compared to control group (P=0.014).

These findings were in agreement with the Lipple *et al.*, 2008 in Germany, who found lower obestatin levels in obese patient with type 2 diabetes compared to control subjects [15], but the variations did not reach the level of statistical significance, and obestatin levels differed according to gender. This difference might be due to variations in environment and the type of food.

A study by Lu *et al.* 2016, who had reported a very similar study found higher obestatin levels in obese patient with type 2 diabetes as compared to controls [18]; this difference might be due to the relatively small number of participants in their study (n:27), and diurnal variations in obestatin production, which had been reported to follow a pulsatile pattern [19].

Obestatin levels in our study correlated inversely and significantly with BMI, insulin, and HOMA- IR values in obese patients with T2D (Fig. **5**). These results suggested that obestatin concentrations could affect insulin resistance and body weight.

However, these findings were in agreement with a previous study(Qi *et al.* 2007), which found that obestatin levels correlated inversely and significantly with BMI (P = 0.035), insulin (P = 0.003) and HOMA-IR (P = 0.031) values, and did not correlate significantly with age (P = 0.162) nor glucose (P = 0.162) in diabetic patients (but their patients were not obese) [20]

A study by Ma *et al.* 2014 found that plasma obestatin concentrations in diabetic patients were significantly lower than those in normal glucose tolerance subjects. This is consistent with our results, although, all their subjects were middle-aged (41-64 years) and old (65-76 years) and they were not obese, and they showed that plasma ghrelin was negatively associated with fasting glucose and Urine Albumin-to-Creatinine Ratio (UACR), so that the lower ghrelin levels might be a potential indicator for renal dysfunction in patients with T2D [21].

Another study by Taskin *et al.* 2015 showed that levels of obestatin were significantly lower in obese group than non-obese and control groups ($p < 0.001$). However, subjects were patients with polycystic ovary syndrome PCOS, and serum copeptin levels were significantly higher in obese PCOS group than they were in non-obese PCOS and control groups ($p < 0.001$) [22].

A study by Huang *et al.* 2014 showed that in the evolution of type 2 diabetes, the increase of visceral fat area could be the initiating factor, leading elevated acyl ghrelin(bioactive form), reduced unacyl ghrelin, insulin resistance, and finally elevated blood glucose [23].

CONCLUSION

Our results suggest that obestatin levels may contribute in body weight regulation and insulin resistance in patients with type 2 diabetes.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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