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Leptin and Soluble Leptin Receptor Among Obese Adults in the Gaza Strip

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ABSTRACT: This study aims to ascertain whether protohormone leptin and soluble leptin receptor (OB-Re) are correlated with Body Mass Index (BMI), gender, serum lipid profiles among adult individuals in the Gaza Strip. Study sample was convenient and obtained from two largest obesity clinics in the Gaza strip. Case group consisted of 83 adult individuals (BMI ≥25 kg/m^2) without history of other diseases. Control group consisted of 83 eligible normal weight adult individuals (BMI 18.5-24.9 Kg/m^2) that was selectively chosen from the same clinics. Self reported structured interviews and serum blood samples were obtained from both groups. Human leptin and soluble leptin receptor were determined by competitive ELISA kits. Logistic data were analyzed by SPSS WIN. The results showed a significant positive correlation between BMI and leptin hormone among the case individuals (r =0.64, P <0.01). In contrast, the results showed that OB-Re has inverse statistical relationship with BMI for the same individuals (r =-0.26, p =0.02). The results, surprisingly, showed no significant correlation between OB-Re and leptin among the case individuals (r =-0.16, p =0.14). For the case individuals, the leptin was also significantly higher (p =0.00) for the females (mean= 72.40 ng/ml) than for the males (mean= 44.05 ng/ml). On the other hand, for the same individuals, OB-Re was slightly higher for the females (mean=9.75 ng/ml) than for the males (mean= 8.91 ng/ml) which was not statistically significant. Serum leptin, cholesterol, triglyceride and LDL-c levels were increased with increasing BMI. Conversely OB-Re and HDL-c were decreased with increasing BMI.

Key words: leptin, soluble leptin receptor, Body Mass Index, gender, lipid profiles, obese adults, the Gaza Strip.

هرمون اللبيتن ومستقبلِه الذائب في الدم لمرضى البدانة البالغين في قطاع غزة

الملخص: تهدف الدراسة للتحقق من وجود علاقة بين هرمون اللبيتن و مستقبله الذائب مع كل من دليل الكتلة، والجنس، ودهون الدم لمرضى البدانة البالغين في قطاع غزة، واشتملت عينة الدراسة على 83 فردا بالغا ($BMI \geq 25\ kg/m^2$) خاليا من الأمراض ذات العلاقة (مجموعة تجريبية)، وعلى 83 فردا بالغا ($BMI\ 18.5\text{-}24.9\ Kg/m^2$) خاليا من الأمراض (مجموعة ضابطة)، و جمعت العينات من خلال المقابلة وتعبئة استبانه، كما سحبت عينات دم لتقدير هرمون اللبيتن ومستقبله الذائب باستخدام تقنية ELISA وكذلك لتقدير الدهون المختلفة، واستخدمت الحزمة الإحصائية SPSS.13 لتحليل البيانات والنتائج التي تم الحصول عليها.

أظهرت النتائج وجود علاقة طردية ذات دلالة إحصائية عند أفراد المجموعة التجريبية بين ارتفاع هرمون اللبيتن وزيادة دليل كتلة الجسم، وعلاقة عكسية ذات دلالة إحصائية بين انخفاض مستقبل اللبيتن الذائب وزيادة دليل كتلة الجسم، وأظهرت الدراسة أيضا أنه لا توجد علاقة ذات دلالة إحصائية بين هرمون اللبيتن ومستقبله الذائب في بلازما الدم لنفس أفراد المجموعة التجريبية، وكذلك تبين وجود فروق ذات دلالة إحصائية في هرمون اللبيتن تبعا لمتغير الجنس، ولم تستطع الدراسة إثبات أي فروق في مستقبل اللبيتن الذائب تبعا لنفس المتغير. بالإضافة إلى ذلك كله أوضحت نتائج الدراسة وجود علاقات طردية ذات دلالة إحصائية بين هرمون اللبيتن وكلا من الكولسترول، والدهون الثلاثية، و البروتين الدهني منخفض الوزن، و كذلك بين مستقبل اللبيتن الذائب و البروتين الدهني عالي الوزن، كما أوضحت النتائج وجود علاقات عكسية ذات دلالة إحصائية بين مستقبل اللبيتن الذائب وكلا من الكولسترول، و الدهون الثلاثية والبروتين الدهني منخفض الوزن، وكذلك بين هرمون اللبيتن والبروتين الدهني عالي الوزن.

INTRODUCTION

Leptin is lately detected adipocytes derived protohormone encoded by the obese (ob) gene with an extremely conserved 167-amino acids [1]. A number of a non-adipocyte tissues have been shown to synthesize and secrete leptin [2-5]. Leptin receptors have been found in several hypothalamic nuclei where genes express one or more neuropeptides and neurotransmitters that influence food intake and/or body weight [6]. Genetic data indicated that the Neuropeptide Y (NPY) and one or more of its receptors act in response to absence of leptin. In contrast, The data also indicated that Melanocyte stimulating hormone (MSH), and its receptors are required for response to an increase in plasma leptin concentration [7].

The OB-Re is a member of the cytokine receptor family [8]. It is encoded by the diabetes (*db*) gene. Leptin receptor mRNA is alternatively

spliced giving at least five transcripts from a single gene. These transcripts encode protein called 1- long (OB-Rb), 2- short (OB-Ra, c, and d), and 3- soluble (OB-Re) forms of leptin receptors [9]. Leptin receptors are expressed in both nervous system and peripheral tissues [10]. Leptin receptor long form is enriched in the hypothalamus, the site of leptin action on food intake and body weight control. Among the short forms of leptin receptor, OB-Ra that may be involved in the transport of leptin across the brain barriers to reach the hypothalamus [11].

Beside long and short OB-Re isoforms, a soluble form (lacking a trans-membrane domain) had also been described [12]. OB-Re makes up the main binding compound of leptin in the blood plasma [13]. In obesity, level of OB-Re is decreased compared with lean control resulting in an increase fraction of free leptin [14]. Moreover, reduction of body weight through diet or surgical procedure significantly increased concentration of circulating OB-Re and thus increased the fraction of bound leptin [15]. Thus, OB-Re may act as a regulating factor of leptin action and plays an important role in leptin resistance.

The BMI (Kg body weight/height in meter square) has been commonly used for measuring the percent of body fat. Thus, differences in BMI between people of the same age and sex are usually due to body fat. According to WHO, its value falls into one of these categories: below 18.5 corresponds to underweight and possibly malnourished, 18.5-24.9 corresponds to healthy normal weight; 25-29.9 indicates overweight, and 30 or above corresponds to obesity. It should be emphasized that, these cut-off values of the BMI are very applicable for Orientals [16].

Obesity in general is multi-factorial disease that develops from the interaction between genotype and the environment. National Institutes of Health (NIH) (1998) reported that there is an association between obesity and other diseases such as cardiovascular, diabetes type II, stroke, cancer, and other diseases [17]. In addition to health effects, obesity has an enormous financial impact [18]. In urban Palestinian population the prevalence of obesity was high, 30% for men and 49% for women [19, 20].

However, while numerous studies have been reported about leptin and its receptors action on regulating body weight [7,12-15], to date no study in the Gaza Strip and the West Bank has been reported about the assessment of leptin and OB-Re among different individuals. Therefore, this study aims to investigate, whether there are relationships between leptin, and OB-Re, BMI, and serum lipid profile levels among adults in the Gaza Strip.

MATERIALS AND METHODS

Study design: The study involved two groups, the case adult individuals (BMI ≥25 kg/m^2), and the control adult individuals (BMI 18.5-24.9 kg/m^2).

Setting and study sample: Two largest obesity clinics from the North and the Mid-Zone Governorates in the Gaza strip were chosen in order to collect a representative samples. About 42% of the subjects were recruited from the specialized herbal center (North Governorate) and about 58 5% of the subjects were from Europe regime center (Mid-Zone Governorate). Study sample was convenient and consisted of 83 overweight adult individuals (40 men and 43 women; mean age (SD) was 36.5 (9.5)) without history of other diseases (case group). The case group was divided into three class, pre-obese (BMI 25-29.9 kg/m^2) class I, obese (BMI 30-39.9 kg/m^2) class II, and extreme obese (BMI ≥ 40 kg/m^2) class III. Class I consisted of 30 individuals (15 men and 15 women), class II consisted of 30 individuals (13 men and 17 women) and class III consisted of 23 individuals (12 men and 11 women). Control group consisted of 83 ideal weight adult individuals (40 men and 43 women; mean age (SD) was 36.3 (9.5)) that selectively chosen from the same places to match case group in age and gender.

Tools of the study: The questionnaire included issues about the following information: age, gender, address, weight and height. Face to face structured interviews that showed high degree of validity and reliability were used to collect data from the case and the control individuals.

Blood sampling and processing: Six ml of 12 hrs fast blood samples were collected from the subjects in plastic centrifuge tubes without any anticoagulant and the tubes left for a while. After centrifugation at 3000 rpm for 20 min., the separated serum was divided into two plastic tubes. One stored at 2-5°C for no more than 24 hours prior to lipid profile determination, and the other was stored frozen at -70°C for serum human leptin and human OB-Re analysis.

Lipid Profiles analysis: Lipid profile analysis included cholesterol, high density lipoprotein-cholesterol (HDL-c), low density lipoprotein-cholesterol (LDL-c), and triglyceride was carried out using a commercially available diagnostic system (GmbH-Germany) test kits (21-24). .

Serum leptin and leptin soluble receptor analysis methods: Frozen serum samples were thawed at 4-8 ˚C then mixed by gentle shaking at room temperature prior to use. Determination of human leptin and human OB-Re level were carried out by competitive enzyme immunoassay technique using ELIZA kits from Diagnostic System Laboratories (Texas, USA) (25,26).

Data analysis: Data calculation and Graphs were performed using SPSS WIN (Version 13).

RESULTS

Table 1 shows that the mean (SD) serum leptin concentrations among the case individuals, 58.74 (33.55) ng/ml (Table 1), was very heterogeneous and strongly correlated with BMI (r=0.64, p<0.01) (Figure 1). In contrast, the mean (SD) serum leptin concentrations among the control individuals, 13.96 (9.80) ng/ml, was not correlated with BMI (r=0.13, p>0.05) (Table1, Figure 1).

Table 1: Mean (SD) serum leptin, OB-Re, and BMI among the case and the control group.

Variables	Case	Control	p-value
BMI (kg/m^2)	34.70 (7.81)	21.91 (1.81)	0.00
Leptin (ng/ml)	58.74 (33.55)	13.96 (9.80)	0.00
OB-Re (ng/ml)	8.71 (2.76)	15.47 (4.41)	0.00

Table 1 also shows that the mean (SD) serum OB-Re concentrations was 8.71 (2.76) ng/ml which found to have an inverse statistical relationship with BMI among the case individuals (r= -0.26, p= 0.02) (Figure 2). In contrast, for the control group, it was shown that the mean (SD) OB-Re concentrations, 15.47 (4.41) ng/ml, was not statistically correlated with the BMI value (r=0.01, p= 0.99) (Table1, Figure 2).

Figure 3 shows no significant correlation between OB-Re and leptin among the case group (r = -0.16, p = 0.14). This result was most probably due to the small sample size since all the study individuals showed significant negative correlation (r = - 0.51, p<0.01) between the leptin and its soluble receptor (Figure is not shown, see Table 4). In contrast to the results of the case group, Figure 3 shows a significant inverse correlation between leptin and its soluble receptor among the control group (r = -0.23, p = 0.03).

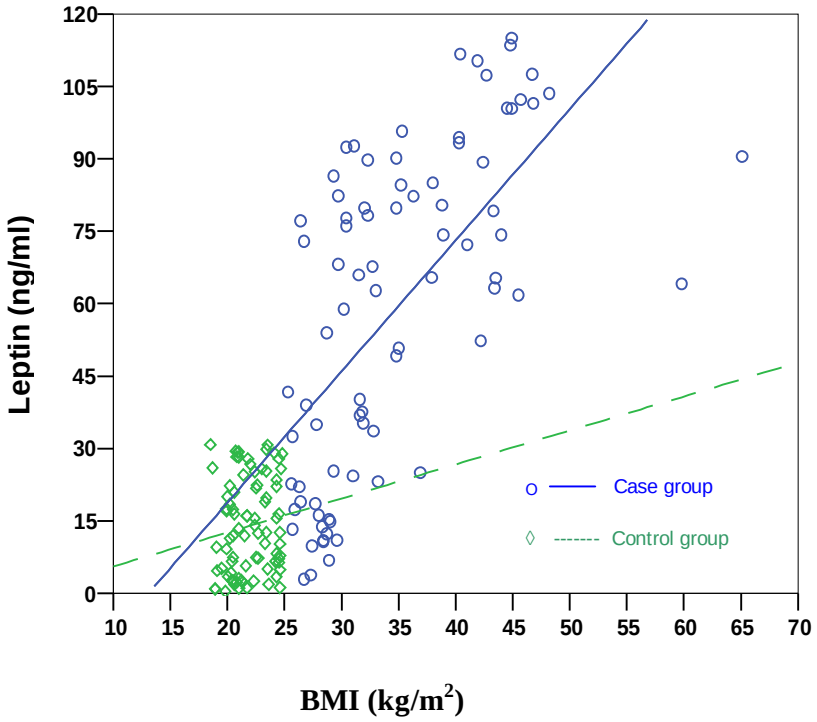

Figure 1: The relationship between leptin and BMI among case and control groups.

Table 2 shows that the mean (SD) leptin levels for the extreme obese, obese, pre-obese, and normal adult individuals were 90.50 (27.6), 64.50 (23.10), 28.90 (24.90) and 13.96 (9.80) ng/ml, respectively. In contrast, the same table shows that the mean (SD) OB-Re levels for extreme obese, obese, pre-obese, and normal adult individuals were 7.30 (2.20) , 9.30 (4.30) , 10.90 (3.10), and 15.47 (4.40) ng/ml, respectively .

Table 2: Mean (SD) serum Leptin and OB-Re among obesity classes and the control.

Parameters	**Ext.Obese (N= 23) BMI ≥ 40**	**Obese (N= 30) BMI 30-39.9**	**Pre-obese (N= 30) BMI 25-29.9**	**Normal (N= 83) BMI 18.5-24.9**
Serum leptin (ng/ml)	90.50 (27.60)	64.50 (23.10)	28.90 (24.9)	13.96 (9.80)
OB-Re (ng/ml)	7.30 (2.20)	9.30 (4.30)	10.90 (3.10)	15.47 (4.40)

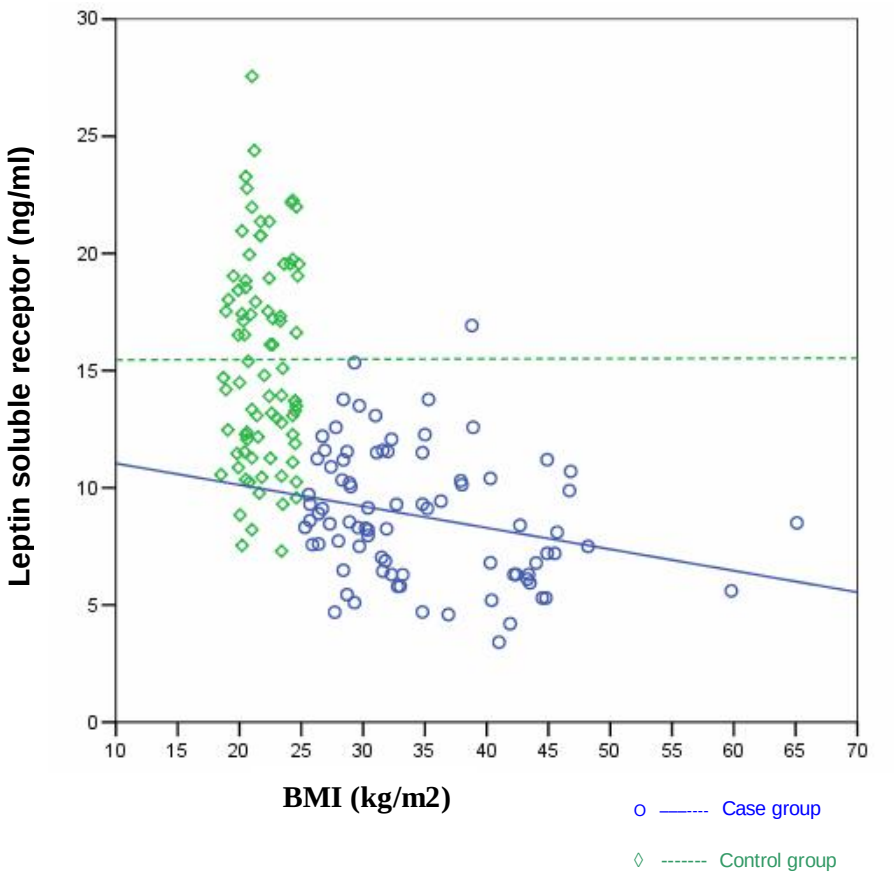

Figure 2: The relationship between OB-Re and BMI among the case and control groups.

Table 3 shows that, the leptin was significantly higher in the females than in the males (p =0.00) for the case group. In contrast, for the same group, OB-Re did not support the hypothesis that OB-Re differs in both sexes as revealed by the p =0.41. Similar to the case group, Table 3 shows that leptin for the control group was significantly higher in the females than the males (p= 0.01). In contrast OB-Re level of the control group was not different in both sexes as revealed by the p =0.85.

Table 3: Mean (SD) serum leptin and OB-Re levels among adult male and female individuals.

	Serum leptin (ng/ml)		OB-Re (ng/ml)	
Sex	Case	control	case	control
M. (N= 40)	44.05	6.20	8.91	16.40
F. (N= 43)	72.40	21.10	9.75	14.50
p-value	0.00	0.01	0.41	0.85

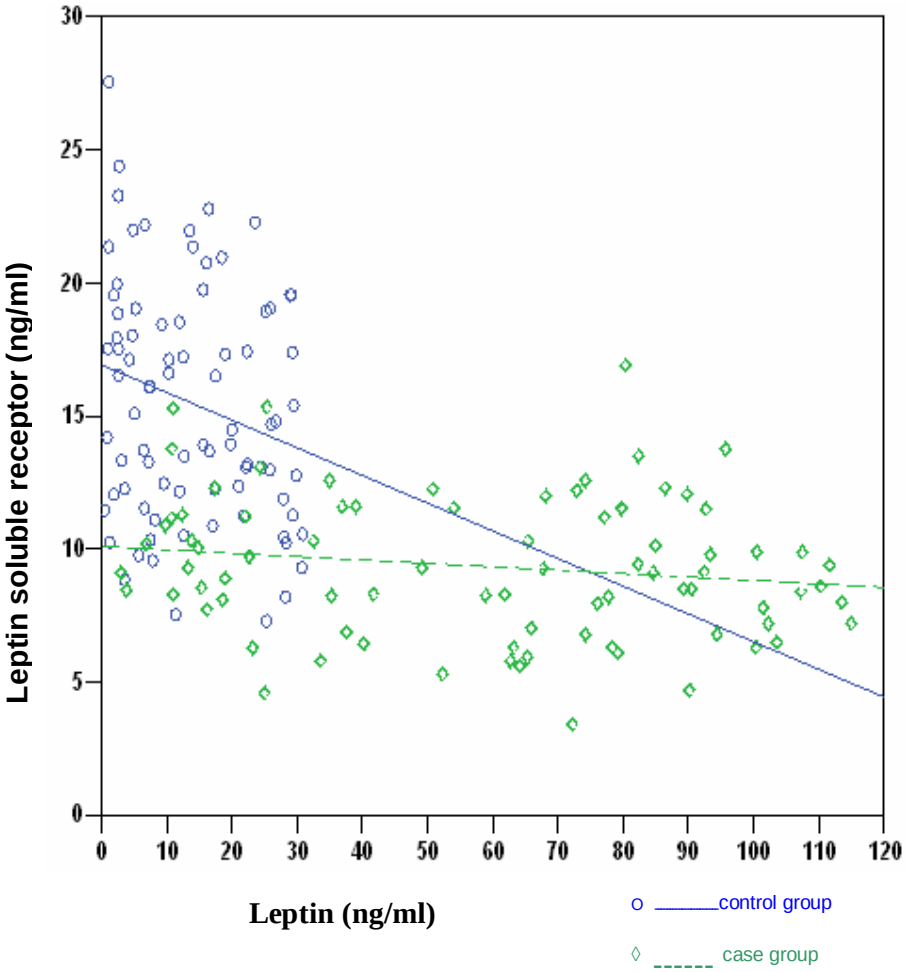

Figure 3: The relationship between leptin and OB-Re among the case and control groups.

Table 4 shows that serum leptin, cholesterol, triglyceride and LDL-c levels were increased with increasing BMI. Conversely OB-Re and HDL-c were decreased with increasing BMI. A significant positive correlation was found between OB-Re and HDL-c. In addition, a significant positive correlation were found between cholesterol, LDL-c, and triglyceride with leptin. Significant negative correlation were detected between leptin, cholesterol, LDL-c, and triglyceride with OB-Re. Moreover a significant negative correlation was found between HDL-c and leptin.

Table 4: Pearson correlation coefficients of leptin, leptin soluble receptor, BMI and lipid profile levels among all study subjects.

Variables	BMI	Leptin	Chole-sterol	HDL-c	LDL-c	Triglyceride
BMI	1.00	0.80**	0.41**	-0.40**	0.36**	0.54**
Leptin	0.80**	1.00	0.40**	-0.23**	0.36**	0.38**
OB-Re	-0.58**	-0.51**	-0.20**	0.37**	-0.18*	-0.41**

*significant ($p < 0.05$), ** highly significant ($p < 0.01$).

DISCUSSION

The study results showed that obese adult individuals had higher serum leptin and lower serum OB-Re levels than normal body weight adult individuals. It also showed that serum leptin level was directly correlated with BMI (Figure 1, Tables1, and 2) whereas OB-Re level was inverse correlated with BMI (see also Figure 3). These results are consistent with very recent studies which demonstrated that circulating leptin levels in human are very heterogeneous and positively correlated with percent body fat [27-29]. In contrast, Considine et al. (1996) reported that the mean (SD) serum leptin concentrations were 31.3 (24.1) ng/ml in obese subjects and 7.5 (9.3) ng/ml in normal weight subjects (28). These differences in leptin values may be due to differences in sample size and age of the subjects used. Similar to our findings, Popruk et al. (2005) reported that the median serum leptin levels of overweight and obese females were significantly higher than those of males in the same group. Moreover, the median OB-Re of overweight and obese females did not show any significant difference between the two sexes [29]. The reduction in OB-Re in the obese

individuals might reflect a negative regulation of leptin. It was also reported that during weight reduction, leptin levels decreased, whereas OB-Re levels and the receptor bound fraction of free leptin increased [30]. The leptin that is bound by its soluble receptor appears to be inactive but may become accessible for release into circulation and activates leptin response [31, 32]. More recently, it has been found that human obesity represents a resistance state to leptin. Resistance is likely caused by a combination of resistance at the receptor and post-receptor levels as well as a decreased ability of the blood-brain barrier to transport circulating leptin into the brain. [33].

In the case and the control adults, the average of serum leptin levels among the females were significantly higher than those of the males (Table 3). This can reflect gender differences in body composition and fat distribution. In women fat accumulated in the gluteal and femoral regions while men have preferential abdominal accumulation [34]. Conversely, for either study group, the mean of serum OB-Re levels for the females was not significantly different from males (Table 3).

The study also examined whether leptin and OB-Re are statistically correlated with lipid parameters among all study subjects (Table 4). It was found that similar to BMI, serum leptin levels were positively correlated with triglyceride, cholesterol and LDL-c. An inverse relationship was found between leptin and HDL-c. Conversely serum OB-Re levels were negatively correlated with cholesterol, LDL-c and triglyceride. In contrast to leptin, OB-Re was also positively correlated with HDL-c. It can be concluded that leptin production occurs mainly in adipocytes and is highly related to lipid profiles. Increasing OB-Re may be one factor operating in the lowering risk of obesity related diseases. Cholesterol and triglyceride are transported in the body fluids in the form of lipoprotein particles. The relationships between serum leptin concentrations, OB-Re concentrations, lipids and lipoproteins are not so clear. It was reported that school children with higher plasma leptin levels have significantly higher triglyceride, LDL-c and apoprotein A levels than those with relatively lower leptin levels [35]. In contrast, It was demonstrated that a relationship between leptin concentrations and lipid profile and lipoprotein levels among hyper-lipidemic adult patients was not statistically significant [36].

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