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Relationship between leptin and insulin action in adult men

Sokhanguei Yahya

University of Social Welfare and Rehabilitation Sciences, Iran

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Abstract

There is considerable evidence that obesity is associated with systemic inflammation, but the underlying mechanisms of these associations are largely unknown. In this study, we evaluate serum leptin in relation to insulin function in obese men. For this purpose, fasting serum level of leptin, insulin and glucose were measured in thirty five non-trained adult men (aged, 35 ± 5.7 years; Body mass index, 32.9 ± 3.4 kg/m2). Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and insulin sensitivity (HOMA-IS) were calculated by the fasting blood glucose and insulin. Pearson correlation method used to determine the relationship between serum leptin with insulin resistance and insulin sensitivity in studied subjects. Data analysis showed that serum leptin was positively related with insulin resistance ($p = 0.003$, $r = 0.50$) and negatively related with insulin sensitivity ($p = 0.014$, $r = 0.43$) in studied subjects. We conclude that serum leptin measuring can be precise predictor of insulin action in obese individuals.

* **Corresponding Author:** Sokhanguei Yahya ✉ sokhanguei0102@yahoo.com

Introduction

The factors that promote insulin dysfunction and increase the incidence insulin resistance in obese subjects or its related disorders are not fully understood. Higher levels of insulin and inflammatory mediators in obese people than normal weight individuals were reported by some previous studies (Myers, 2004). This finding supports of a higher insulin resistance or lower insulin sensitivity in these population than normal weight subjects, although the physiopathological mechanisms underlying of any association between insulin function and adipokines such as leptin are largely unknown.

Leptin is a peptide hormone derived adipose tissue with molecular weight of 16 kDa whose concentration varies depending on the body fat levels and affects glucose metabolism and insulin sensitivity (Anissa *et al.,* 2006). It was reported that leptin resistance is one of the factors affecting hyperinsulinemia and ultimately glucose intolerance in obesity or its related diseases (Morioka *et al.,* 2007). The presence of hyperglycemia and hyperphagia in obese individuals, despite high levels of insulin and leptin, suggests these individuals are resistant to the actions of both hormones (Myers, 2004). The inhibitory effect of leptin on insulin gene expression as well as insulin secretion from pancreatic beta cells in humans and animal models was reported by some previous studies (Kieffer *et al.,* 2000; Poitout *et al.,* 1998).

Animal studies have provided evidence indicating that mice with disrupted leptin signaling in β cells display hyperinsulinemia, insulin resistance, glucose intolerance, obesity, and reduced fasting blood glucose (Wang *et al.,* 2010). These authors noted that insulin resistance of these mice is due to excessive insulin secretion from pancreatic β cells (Gray *et al.,* 2010). On the other hand, the finding of a recent study showed that serum leptin can not affect insulin secretion of beta cells (Koebnick *et al.,* 2008). Despite these statements, the effects of some adipokines such as leptin on insulin sensitivity, insulin secretion and beta-cell function are less understood. Therefore, this study aimed to evaluate relationship between serum leptin with insulin, insulin resistance and insulin sensitivity in a group of adult men.

Materials and methods

Subjects

This study was aimed to determine relation between fasting serum leptin with insulin resistance and insulin sensitivity in thirty five non-trained adult men (aged, 35 ± 5.7 years; Body mass index, 32.9 ± 3.4 kg/m2) that participated in study by accessible sampling. The study was conducted with the approval of the Ethics Committee of University of Social Welfare and Rehabilitation Sciences, Iran. Each participant received written and verbal explanations about the nature of the study before signing an informed consent form.

Inclusion and exclusion criteria

None of the subjects had participated in regular exercise/diet for the preceding 6 months, nor did all subjects have stable body weight. Participants were non-athletes, non-smokers and non-alcoholics. Subjects were excluded if they had a known history of cardiovascular disease, stroke or transient ischemic attack, uncontrolled hypertension, liver disease, renal disease, diabetes or asthma, or any other serious chronic disease requiring active treatment. Those that were on medications known to alter fasting glucose or insulin were excluded.

Anthropometric and biochemical measurements

Anthropometric measurements of height, weight, percent body fat, and circumference measurements were taken in a fasting state when the participant had thin clothes on and was wearing no shoes. Height and body mass were measured using a wall- mounted stadiometer and a digital scale, respectively. Abdominal circumference was measured with a non-elastic tape at a point midway between the lower border of the rib cage and the iliac crest at the end of normal expiration. Body fat percentage was determined using body composition monitor (OMRON, Finland). The Body Mass index (BMI) was

calculated using the formula body weight/height2 in terms of kg/m².

All blood samples were taken following an overnight 12-hour fast. Blood samples were obtained in order to measuring serum leptin, insulin and glucose concentration after an overnight fast. Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and insulin sensitivity (HOMA-IS) were calculated by the fasting blood glucose and insulin (Matthews *et al.,* 1985). Serum leptin was determined by ELISA method, using a Biovendor- Laboratorial kit made by Biovendor Company, Czech. Glucose was determined by the oxidase method (Pars Azmoon kit, Tehran). Insulin was determined by ELISA method (Demeditec, Germany).

Statistical analysis

All values are given as mean and standard deviation. Statistical analysis was performed with the SPSS software version 15.0. The Kolmogorov-Smirnov test was applied to determine the variables with normal distribution. Pearson correlation method used to determine the relationship between serum leptin with insulin resistance and insulin sensitivity in studied subjects. All statistical tests were performed and considered significant at a $P \leq 0.05$.

Results

Previously noted in the methods section that the objective of this study was to determine the relation between serum leptin with insulin resistance and insulin sensitivity in adult healthy obese men. Table 1 presents the circulating, fasting concentrations of biochemical variables and anthropometrical characteristics in study subjects. Experimental data are presented as means ± SD.

Table 1. The descriptive anthropometric and biochemical features of studied subjects.

Variable	Mean	Standard deviation
Age (years)	35	5.7
Weight (kg)	102	15.4
Height (cm)	176	7.11
Abdominal circumference (cm)	105	7.11
Body mass index (kg/m²)	32.9	3.4
Body fat (%)	31.8	4.18
Systolic blood pressure (mmHg)	129	21
Diastolic blood pressure (mmHg)	88	15
Glucose (mg / dl)	102	9.68
Insulin (µIU/ml)	8.39	2.91
Insulin resistance (HOMA-IR)	2.12	0.76
Insulin sensitivity (HOMA-IS)	0.62	0.07
Serum Leptin (µg/ml)	18.29	9.47

The data analysis of Pearson method showed a significant positive correlation between insulin resistance and serum leptin in studied subjects ($p = 0.003$, $r = 0.50$). Serum leptin levels were significantly correlated with insulin levels ($p = 0.003$, $r = 0.51$), but not to fasting glucose ($p = 0.918$, $r = 0.02$). Serum Leptin also negatively correlated with insulin sensitivity in studied subjects ($p = 0.014$, $r = 0.43$).

Discussion and conclusion

The findings clearly show that serum leptin is positively related with insulin resistance. Negative significant relation of leptin with insulin sensitivity was another finding of present study. These findings

support an important role of leptin as an inflammation cytokine on insulin action. On the other hand, systemic leptin can be affecting the sensitivity of body cell to insulin. So increased circulating leptin reduces insulin sensitivity or accompanied with increased insulin resistance in these population. The relationship between leptin or other adipokines or cytokines were reported by some previous studies.

A large body of evidence suggests that Obesity is associated with several metabolic disorders such as type 2 diabetes, dyslipidaemia, atherosclerosis and hypertension, which are major components of the metabolic syndrome. White adipose tissue metabolism and adipose tissue -derived factors such as fatty acids and adipokines play an important role in the development of these metabolic disturbances (Moreno-Aliaga *et al.,* 2010). In fact, dysregulated adipokine secretion from the expanded white adipose tissue of obese individuals contributes to the development of systemic low-grade inflammation, insulin resistance and metabolic syndrome (Moreno-Aliaga *et al.,* 2010).

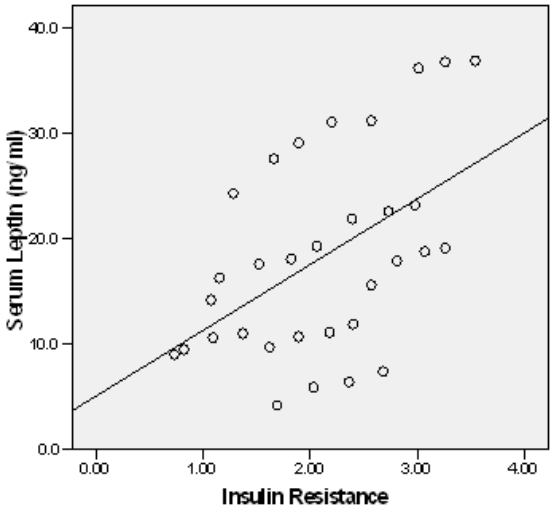

Fig. 1. The correlation pattern between serum leptin and insulin resistance in studied subjects.

While the mechanisms that hasten the onset of diabetes in obese individuals are still not completely elucidated, it is likely that the adipose derived hormone leptin plays a central role in this phenomenon. Leptin has been long known as one of the most important cytokines secreted by adipose, and it plays vital roles in controlling food intake and body energy balance (Sadaf *et al.,* 2000). According to the population studies, it has been indicated that Leptin or leptin-receptor-deficient mice exhibit severe obesity and diabetes (Friedman *et al.,* 1998).

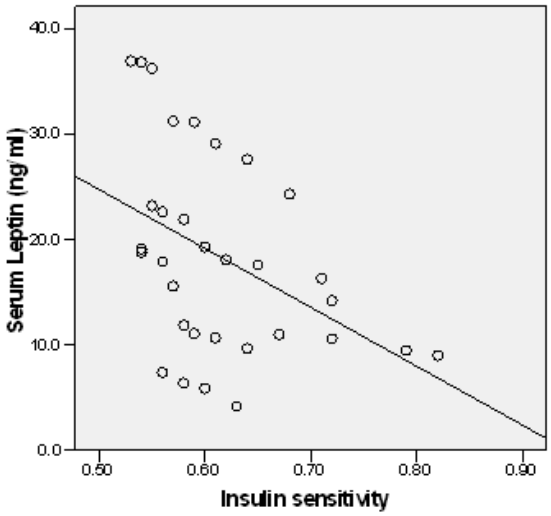

Fig. 1. The correlation pattern between serum leptin and insulin sensitivity in studied subjects.

Recent epidemiologic studies have demonstrated that leptin production occurs after increases in insulin in response to feeding, and that a decrease in leptin concentrations follows insulin declines during fasting (French *et al.,* 2000). Our study results showed a positive relation in serum leptin with insulin concentration. Based on this data, it is likely increased circulating leptin can be affects insulin secretion of pancreatic beta cell. To support of these data, it has been previously reported that mice with disrupted leptin signaling in *β* cells display hyperinsulinemia, insulin resistance, glucose intolerance, obesity, and type II diabetes. These authors noted that insulin resistance of these mice is due to excessive insulin secretion from pancreatic *β* cells (Gray *et al.,* 2010). In contrast, some previous studies in vitro have reported inhibitory effects of leptin on insulin gene expression and insulin secretion in β cell lines and isolated murine and human islets (Kieffer *et al.,* 2000l Kulkarni, 1997; Poitout *et al.,* 1998). On the other hand, some sources have pointed leptin is significant and independent predictor of insulin sensitivity, but not of insulin secretion or beta-cell function in overweight Hispanic youth (Koebnick *et al.,* 2008).

In obese individuals, increased fat mass is associated with hyperleptinemia and increasing leptin resistance which refers to negative correlation between leptin and insulin sensitivity (Zhang *et al.,* 2006). One study reported that leptin is an independent negative predictor of insulin sensitivity (p 44). The finding of another recent study showed that among cytokines, serum leptin was only having a strong significant association with insulin resistance (Peti *et al.,* 2010). The presence of the leptin receptor in pancreatic cells suggests that leptin might be an adipose tissue signal to alter insulin secretion in states of increased fat depots and decreased insulin sensitivity (Seufert *et al.,* 1999).

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