

RELATIONSHIPS OF SERUM LEPTIN CONCENTRATION WITH INSULIN, GLUCOSE, HbA1c LEVELS AND INSULIN RESISTANCE IN OVERWEIGHT POST-MENOPAUSAL DIABETIC WOMEN

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Abstract

BACKGROUND: Leptin, the product of the ob gene, could have a role in the pathogenesis of obesity and non-insulin dependent diabetes mellitus (NIDDM). The aim of this study was to investigate relationships between serum leptin concentration and insulin, glucose, HbA1c levels and insulin resistance in diabetic women.

METHODS: We studied 45 diabetic women and 45 healthy women (controls) who aged 45-60 years and had BMI of 25-30 kg/m². Serum leptin, insulin, HbA1c, fasting blood sugar and insulin resistance were determined in the two groups.

RESULTS: There was a significant positive correlation between leptin and insulin ($r = 0.295$, $P = 0.049$) and insulin resistance ($r = 0.329$, $P = 0.027$) in controls but non-significant correlation between leptin and HbA1c and fasting blood sugar were observed in the two groups.

CONCLUSION: This study did not document any significant relationship between serum leptin and insulin, glucose, HbA1c and insulin resistance in diabetic women.

Keywords: Type 2 Diabetes Mellitus, Leptin, Insulin.

ARYA Atherosclerosis Journal 2010, 5(4): 175-180

Date of submission: 4 Aug 2009, *Date of acceptance:* 20 Dec 2009

Introduction

Obesity and associated diabetes are epidemic throughout the world. Diabetes mellitus is a group of disorders that is increasing due to population growth, aging, urbanization, and increasing prevalence of obesity and physical inactivity.¹

Leptin, an ob gene product, is thought to be a lipostatic signal that contributes to body weight regulation through modulation feeding behavior or energy expenditure or both.² It has been suggested that administration of leptin increases energy expenditure and decreases appetite by de-

creasing hypothalamic levels of orexigenic neurotransmitters.³ A variety of hormonal factors such as insulin can also influence circulating leptin levels.⁴ Leptin concentrations have been shown to correlate with insulin concentration and the degree of insulin sensitivity, and a role for leptin has been proposed in the aetiology of insulin resistance and non-insulin dependent diabetes mellitus (NIDDM).^{5,6}

To assess the possible relationship between leptin concentration and insulin, glucose, HbA1c levels and insulin resistance in diabetic women, we stud-

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ied overweight diabetic and healthy women. Only postmenopausal women were included in the study.

Materials and Methods

Subjects and procedures

We studied the following groups of women: 45 women with type 2 diabetes (experimental); and 45 healthy women (control). All subjects provided written informed consent before the study. Diabetes was diagnosed according to the National Diabetes Data Group criteria.⁷ All diabetic patients were taking oral hypoglycemic agents. Subjects who had a body mass index (BMI) between 25 and 30 kg/m², and were aged between 45 and 60 years included. None had ever received hormone replacement therapy. Exclusion criteria included having renal or cardiovascular disease or hypertension, having smoking habits, or using lipid lowering therapy or zinc supplement.

After 12 hours of overnight fasting, venous blood samples of the subjects were drawn into tubes without Li-heparin. Blood samples of 1 ml were used for the determination of glycated hemoglobin (HbA1c). The remaining blood was then centrifuged at 1500_g for 10 minutes in a refrigerated centrifuge, and serum was obtained.

Serum leptin concentration was determined by ELISA assay using a human Leptin ELISA kit (Biovendor Laboratory Medicine, Modrice).

The homeostasis model assessment-insulin resistance (HOMA-IR) score was estimated to show the insulin resistance by using the following for-

mula: (fasting insulin [AU/ml]-fasting glucose [mmol/L]) / 22.5.⁸

Higher HOMA-IR scores indicate lower insulin sensitivity. Serum glucose levels were determined by enzymatic methods using commercial kits (Zist Shimi). HbA1c levels were assayed by Colorimetric Assay (M. Parker).⁹ Serum insulin levels were measured by ELISA assay using a DRG Insulin Enzyme Immunoassay kit (DRG, Germany).

Statistical analysis

Values are expressed as mean \pm SE. Comparisons were performed with the t test. Pearson correlation was used to evaluate the relations among different variables. Differences were considered to be significant at the level of $P < 0.05$.

The research was undertaken under the medical ethics standards.

Results

Table 1 lists the general serum characteristics of groups studied. There was no significant difference in age, BMI and duration of menopause between two groups. Subjects with diabetes had significantly higher serum glucose and HbA1c than control subjects ($P < 0.001$). HOMA-IR scores were also significantly higher in diabetic subjects (3.66 ± 0.33 , $P = 0.001$). On the other hand, control subjects had significantly higher serum leptin (7.76 ± 0.49) levels than diabetic subjects (9.33 ± 0.61).

Table 1. General and serum characteristics of diabetic and healthy women (means \pm SE)

Characteristic	Diabetic group (n = 45)	Control group (n = 45)	P
Age (y)	54.13 \pm 0.44	52.78 \pm 0.72	0.113
BMI (kg/m ²)	27.67 \pm 0.26	27.47 \pm 0.3	0.607
Duration of menopause (y)	4.96 \pm 0.36	3.82 \pm 0.57	0.378
Serum glucose (mg/dl)	168.62 \pm 7.5	93.76 \pm 1.7	< 0.001*
HbA1c (%)	8.61 \pm 0.24	6.23 \pm 0.12	< 0.001*
Serum insulin (μ IU/ml)	8.7 \pm 0.68	10.42 \pm 0.44	0.03**
HOMA-IR	3.66 \pm 0.33	2.43 \pm 0.12	0.001*
Leptin (ng/ml)	7.76 \pm 0.49	9.33 \pm 0.61	0.046**

* $P < 0.001$

** $P < 0.05$

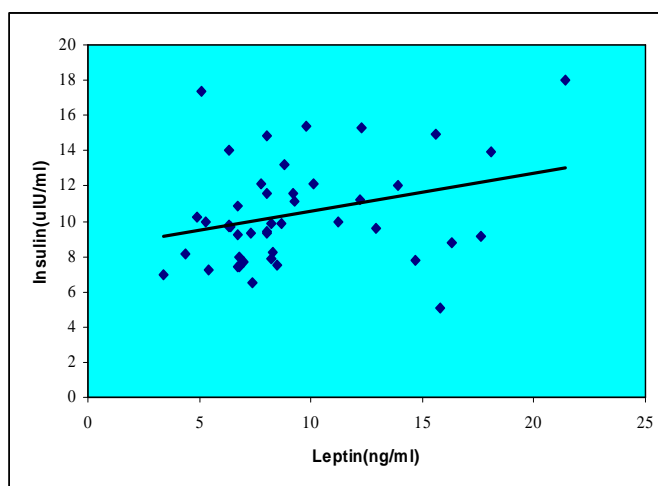
Table 2. Correlations between serum leptin levels and other parameters

Parameters	Diabetic subjects (n = 45)		Controls (n = 45)	
	r	P	R	P
Serum glucose (mg/dl)	-0.152	0.317	0.258	0.087
HbA1c (%)	-0.03	0.843	0.224	0.14
Serum insulin (μIU/ml)	0.206	0.057	0.295	0.049*
HOMA-IR	0.17	0.263	0.329	0.027*

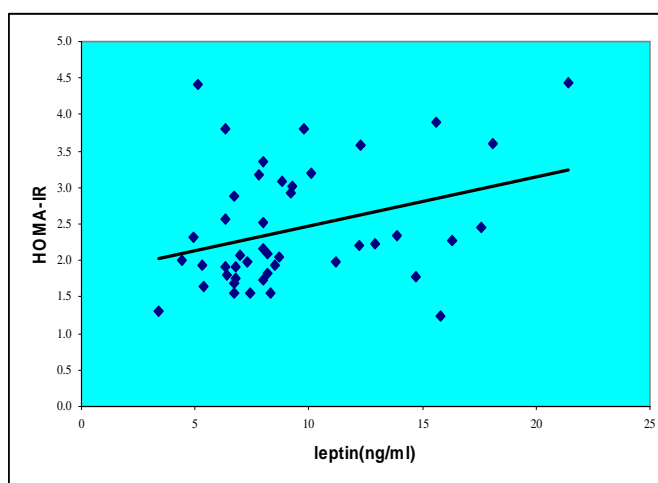
* P < 0.05

Correlation analyses were performed between leptin and the parameters in diabetic and control subjects (Table 2). There were positive correlations between leptin and insulin and insulin resistance in the two groups (r = 0.295, P = 0.049 and r = 0.329, P = 0.027, respectively) (Figure 1 (A, B) and 2 (C, D)). A non-significant negative relation-

ship was found between leptin and HbA1c and fasting blood sugar in diabetic subjects (r = -0.03, P = 0.843 and r = -0.152, P = 0.317, respectively) and a non significant positive relationship was between leptin and HbA1c and fasting blood sugar in the control group (r = 0.224, P = 0.14 and r = 0.258, P = 0.087, respectively).

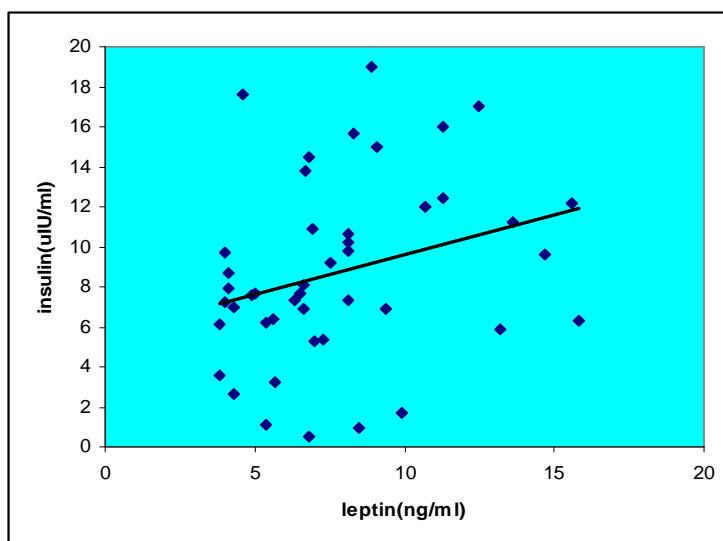


(A)

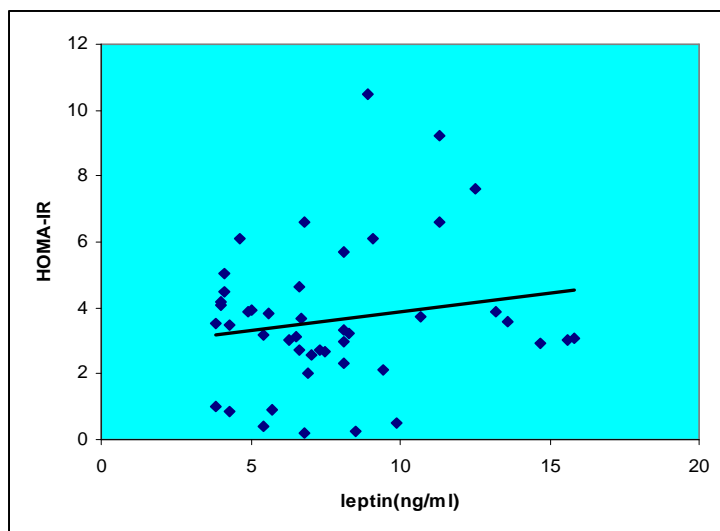


(B)

Figure 1. Plots of plasma leptin concentrations and insulin (A) and insulin resistance (B) in control group.



(C)



(D)

Figure 2. Plots of plasma leptin concentrations and insulin (C) and insulin resistance (D) in diabetic group.

Discussion

This study investigated relationships between leptin and some biochemical parameters that are important in diabetic patients. The main result of the present study is that leptin concentrations were lower in diabetic subjects than control. Some correlates of the so-called metabolic syndrome are associated with this parameter in the two groups. The intrinsic nature of a cross sectional study like this one, however, does not allow one to draw conclusions on the causal relationship between

leptin and other variables.

It has been shown that serum leptin concentration is positively associated with insulin in diabetic and healthy subjects.^{5,10-14} Some studies have shown that long-term exogenous hyperinsulinaemia increases ob gene expression that leads to elevate leptin concentrations in both humans and animal models.^{15,16} The relationship between the two hormones seems to be reciprocal; it has been demonstrated that leptin reduce the insulin secretion and the expression of proinsulin mRNA by

effecting on pancreatic β -cell.⁶ In fact, there is a negative feed-back loop between insulin secretion and leptin synthesis, which could be involved in the pathogenesis of the NIDDM.^{17,18} We observed a positive relationship between insulin and leptin in our two groups but it was significant only in control.

It has also been demonstrated that serum leptin concentration is positively associated with insulin resistant in diabetic and healthy subjects.^{5,12,14,19} Previous reports have been described that elevated leptin levels, independent of BMI, is associated with insulin resistance in lean and obese non-diabetic individuals²⁰. It has been shown that the increased leptin levels, caused by obesity, leads to insulin resistance by interfering with insulin signaling.²¹ In fact, it has been found that leptin inhibits insulin receptor autophosphorylation.²² Our study, like the others, showed a positive relationship between leptin and insulin resistant in the two groups, but it was significant only in control group.

We observed, like in the other studies, a negative relationship between leptin and glucose in diabetic subjects,^{11,12,23,24} but it was not significant. It has been suggested that, in subjects with NIDDM, both glucose and insulin regulate the synthesis of leptin by adipose tissue. These findings show that there may be a relationship between reducing of leptin and increasing adiposity and worsening metabolic control in individuals with NIDDM.¹²

On the other hand, there is a positive relationship between leptin and glucose in healthy subjects.²⁵⁻²⁹ In our study this relation was not significant. When blood glucose reduces, it may decrease secretion of leptin by acting as an inhibitory signal to the adipocyte. Prolonged hypoglycemia counteracts the stimulatory effect of hyperinsulinemia on leptin levels. The evidence that hypoglycemia (induced by hyperinsulinemia) inhibits rises in leptin supports the hypothesis that falling glucose levels during a prolonged fast, directly or indirectly, signals the adipocyte to reduce leptin secretion.³⁰

It has been shown that serum leptin concentration is negatively associated with HbA1c in dia-

betic subjects.^{24,31} We observed a negative relationship between leptin and HbA1c in diabetic subjects, too, but it was not significant. In fact, chronic hyperglycemia could reduce leptin levels at rest.²⁴ This suggests that low levels of leptin with type 2 diabetes, in addition to further contributing to obesity, could also directly increase insulin resistance and thereby worsening the condition.³⁰

Conclusion

In summary, there were not significant relationships between serum leptin and insulin, glucose, HbA1c and insulin resistance in overweight postmenopausal diabetic women.

Acknowledgments

We want to thank Fariba Fatehi and Mahnaz Zarei for their assistance in the field.

Conflict of Interests

Authors have no conflict of interests.

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