



CLINICAL RESEARCH

Leptin Level in Women with Metabolic Syndrome

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Abstract

A detailed study of the dynamics of leptin in the various types of disturbances in carbohydrate metabolism could reveal its role in the pathogenesis of Type 2 Diabetes Mellitus (T2DM).

The aim of this study was to investigate the Fasting Leptin Level (FLL) and effect of acute hyperinsulinemia during the Intravenous Glucose Tolerance Test (IVGTT) on the leptin levels in women with Insulin Resistance Syndrome (IRS).

Materials and Methods: In total, 59 obese women (54.0 [48.5-60.0] yrs; BMI – 33.2 [29.0-37.2] kg/m²) with IRS (12 – obesity (NGT), 18 - ITG and 30 - T2DM) were observed. The IVGTT test was done only in women with impaired glucose tolerance (IGT) and T2DM. The leptin level was investigated during fasting conditions and again 120 min post glucose loading. Then the Hepatic glucose production Index (H-index) was calculated using the IVGTT data.

Results: The FLL in women with normal glucose tolerance (NGT) was almost two times greater than in women with IGT and T2DM. A negative relationship was found to exist between FLL and HbA1c in T2DM ($r=0.3$, $p<0.05$). A positive correlation ($r=0.3$, $p<0.05$) was also recorded between FLL and the H-index in compensated T2DM women (HbA1c<7%), a negative correlation ($r=0.3$, $p<0.05$) was recorded between FLL and the H-index in decompensated T2DM women (HbA1c>8%). The leptin level significantly decreased at 120 min of IVGTT in both the IGT and T2DM groups ($p<0.05$).

Conclusion: The FLL depended upon the degree of glucose metabolism impairment; postprandial leptin response to the glucose load was lower in the IGT group than in the T2DM subjects.

Keywords: leptin, IVGTT, T2DM, IGT.

Introduction

Adipose tissue is the site where several hormones and biologically active peptides, including leptin and adiponectin, are synthesized. Leptin is found to suppress the appetite, probably by decreasing the orexigenic neuropeptide Y in the hypothalamus. The antisteatogenic effect of leptin prevents the ectopic lipid storage associated with insulin resistance. Recent studies have demonstrated that leptin affects the carbohydrate metabolism by facilitating the glucose uptake in the skeletal muscles and adipose tissue [1] and suppressing the hepatic glucose production (HGP). Leptin has also been demonstrated to decrease the HGP by at least two mechanisms: (a) inhibition of gluconeogenesis from lactate and (b) suppression of glycogenolysis [2].

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Loading with glucose and insulin is associated with an increase in the leptin mRNA and circulating leptin levels [3]. The postprandial leptin secretion affecting satiety, free fatty acid oxidation and glucose elimination to the muscles and adipose tissue are of special interest to the investigators. Alterations in the leptin secretion during the fasting and post loading states could play a role in the pathogenesis of Type 2 Diabetes Mellitus (T2DM).

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The aim of this study was to investigate the Fasting Leptin Level (FLL) and effect of acute hyperinsulinemia during the Intravenous Glucose Tolerance Test (IVGTT) on the leptin levels in women with Insulin Resistance Syndrome (IRS).

Material and Methods

In total, 59 obese women (54.0 [48.5-60.0] yrs; the body mass index (BMI) – 33.2 [29.0-37.2] kg/m²) with IRS were

observed. Based on the type of glucose metabolism abnormality, all the observations were categorized under three groups: NGT, IGT and T2DM. Age and BMI were similar in all three groups (Table 1).

Table 1.
Characteristics of study participants

| Parameters | Obesity & NGT (n=12) | Obesity & IGT (n=17) | Obesity & untreated T2DM (n=30) |
|------------------------|----------------------|----------------------|---------------------------------|
| Age, yrs | 50.5[43.5-54.7] | 56.0[48.0-57.0] | 57.5[50.0-62.5] |
| BMI, kg/m ² | 32.9[29.7-37.8] | 30.4[26.05-36.6] | 32.7[29.1-37.1] |
| FL, ng/mL | 42.0[22.0-60.0] | 30.4[26.0-36.6] | 32.7[29.1-37.1] |
| FI, pmol/L | 67.6[42.1-98.3] | 75.5[65.5-103.7] | 73.5[37.0-34.5] |

Glucose, insulin and leptin were measured in the fasting state. IVGTT was performed only for patients with IGT and T2DM. Insulin was measured at 70 min and 120 min after glucose loading.

IVGTT: the intravenous introduction of 40% glucose solution (0.75 g glucose per kg body mass) was performed with subsequent blood sampling for the definition of glucose and insulin levels. The blood sampling scheme was done at the following time schedules: -20, -10, 0 (point of glucose upload), 2, 3, 4, 5, 6, 8, 10, 14, 19, 22, 24, 27, 30, 40, 50, 70, 90, 120, 150, and 180 minutes.

Hepatic glucose production (H-index) was calculated using the author's own computer program, whereas the mathematic model was designed by A.V.Dreval [4].

The results are presented as medians and reveal values corresponding to the 25th and 75th percentiles (Me[25-75]). The Two-Independent-Samples Tests procedure compares two groups of cases with one variable. The bivariate correlations procedure computes the Spearman's correlation coefficient.

Results and Discussion

The median of the leptin level of the entire study population was found to be 27.4[14.3-46.4] ng/mL.

The correlation between FLL and age was seen to be

negative ($r=-0.4$; $p<0.05$). The FLL in patients under 55 years of age was more than twice the value found in patients over 55 years of age ($p<0.05$). The positive relationship was found to exist between FLL and BMI ($r=0.6$; $p<0.0001$). The positive correlation was also recorded between FLL and the fasting insulin level ($r=0.4$; $p<0.05$).

The FLL in women with NGT was almost two times greater than in women with IGT and T2DM (42.0 ng/mL, 29.1[13.5-45.7] and 21.1[13.6-39.0] accordingly) (Table 1.).

The leptin level and HbA1c in T2DM

A negative relationship was found to exist between FLL and HbA1c in T2DM ($r=0.3$; $p<0.05$). The FLL in T2DM women with HbA1c <7.5% was higher than that in women with HbA1c >7.5%.

Leptin and the HGP in T2DM women

The correlation between the FLL and H-index in T2DM women with HbA1c<7% also differed from that in T2DM women with HbA1c>8%.

The positive relationship was found to exist between FLL and H-index in T2DM ($r=0.3$; $p<0.05$) in compensated T2DM women (HbA1c<7%) (Fig.1a), and a strong negative correlation was recorded between FLL and the H-index ($r=-0.7$; $p<0.05$) in decompensated T2DM women (HbA1c>8%) (Fig.1b).

The leptin level in IVGTT test

The leptin level significantly decreased at 120 min of IVGTT test in both the IGT and T2DM groups ($p<0.05$). However, the greatest reduction in the leptin level was found in T2DM compared with that in the IGT women (23% vs 15.3%, $p<0.05$).

We found a positive correlation between a decrease in the leptin levels and the area under the insulin curve (AUC) in IGT women ($r=0.4$; $p<0.05$) (Fig 2a) and T2DM women ($r=0.4$; $p<0.05$) (Fig. 2b).

Discussion

Numerous studies have reported that the leptin level depends on the BMI [5-6]. Our investigation also suggests that the leptin level rises along with BMI. Data regarding the differences between the leptin levels in healthy obese subjects and T2DM

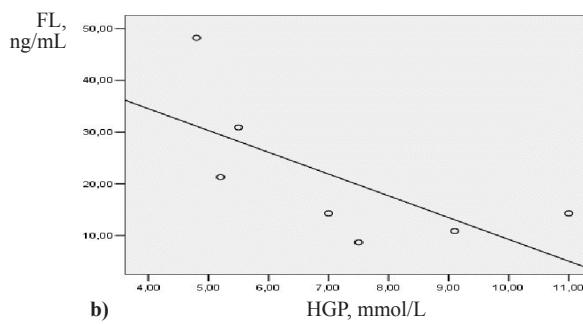
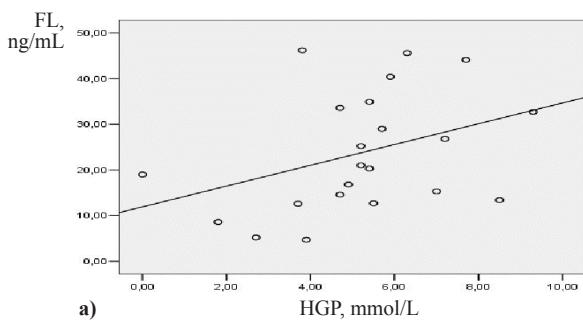
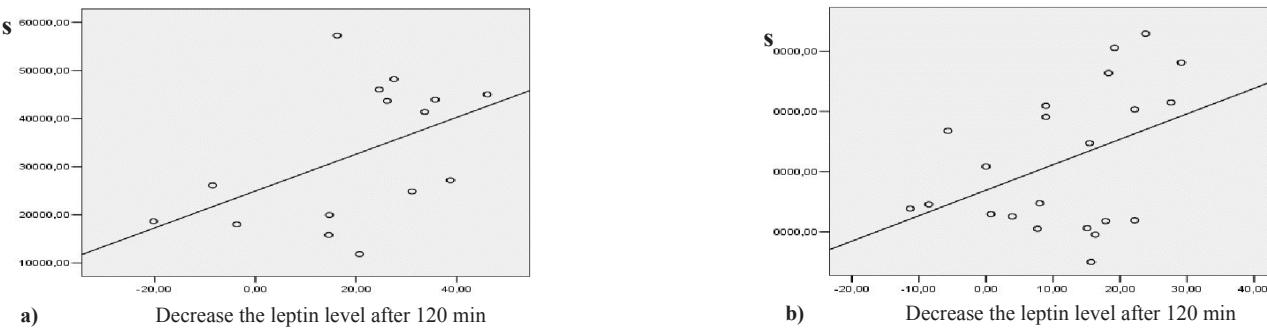


Figure 1.

Relationship between FLL and H-index in T2DM women with different HbA1c: (a) in 21 compensated T2DM women (HbA1c<7%), and (b) in 7 decompensate T2DM women (HbA1c>8%).



Relationship between the decrease in the leptin levels and AUC in 17 IGT women (a) ($r=0.4; p<0.05$) and 30 T2DM women (b) ($r=0.4; p<0.05$). S – area under the insulin curve (AUC).

patients are still not sufficient [5]. In the study conducted by M. Buyukbese et al. [5] no significant differences were found between those parameters. In the study conducted by J. Kolaczynski et al. [7] the fasting plasma glucose concentrations were found to be associated negatively with the leptin levels, independent of BMI, waist circumference or insulin. Moreover, the leptin secretion may be dependent of the utilization of adipocyte glucose, which is clearly attenuated during hyperglycemic crises [8].

In our study, we found out that the leptin levels in healthy obese women was almost twice the value found in women with IGT and T2DM. As leptin production is stimulated by the insulin-independent flux of glucose into the adipose tissues, we posit that the decreased FLL in the IGT and T2DM women is a result of the decreased flux of glucose into the adipose tissues in cases of insulin resistance. These data confirm the low leptin level in T2DM women with $\text{HbA1c}>7.5\%$ compared with that found in IGT women with $\text{HbA1c}<7.5\%$. Therefore, the relationship between the FLL and H-index depends upon disturbances in the glucose metabolism (HbA1c level). In cases of uncontrolled T2DM, the relationship between the FLL and H-index is negative and vice versa. Possibly, the pathogenesis of this phenomenon is associated with lowered leptin secretion because of some impairment in the glucose metabolism.

The results of the assessment of the leptin level post glucose loading are very different. Earlier in our publications we recorded a rise in the leptin levels post glucose loading [9]. Several studies have shown no difference in the leptin levels post glucose loading in lean subjects and a decrease in the leptin levels following a glucose load in obese subjects [10-12].

In our study, we demonstrate a decrease in the leptin level in IVGTT. One explanation is that in the presence of insulin resistance, insulin does not stimulate the leptin secretion properly, post carbohydrate loading [10,13]. This view is supported by the experimental evidence of the lowered stimulatory effect of insulin on the leptin secretion in normal weight men [9].

We found that the degree of decrease in the leptin level is positively correlated with the degree of insulin increase in IVGTT. Thereby, the decreased leptin level post glucose loading in IVGTT is more in the uninjured insulin secretion state. However, the reasons for the relationship between the decrease in the leptin levels and the increase in insulin are not known.

Conclusion

The present study indicates that the FLL depended upon the degree of glucose metabolism impairment; postprandial leptin response to the glucose load was lower in the IGT group than in the T2DM subjects. These results suggest that leptin plays a very important role in the pathogenesis of T2DM and that further studies are warranted to more clearly explain the mechanisms involved.

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