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Taiwanese Journal of Obstetrics & Gynecology 50 (2011) 149–153

www.tjog-online.com

Original Article

Maternal serum leptin concentration in gestational diabetes

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Accepted 23 June 2010

Abstract

Objective: The aim of this study was to evaluate fasting serum leptin concentration and its relation to insulin resistance in women with gestational diabetes mellitus (GDM) and gestational impaired glucose tolerance (IGT).

Materials and Methods: This case-control study, at 28 weeks of gestation, measured serum concentration of fasting leptin, insulin, and homeostatic model assessment index in three groups, GDM, IGT, and normal control, and compared them with each other.

Results: The serum leptin level was significantly higher in women with GDM than in the two other groups ($p = 0.03$). In women with GDM and IGT, leptin was significantly positively related with insulin and homeostatic model assessment index ($r = 0.221$, $p = 0.03$) and ($r = 0.246$, $p = 0.03$), respectively. In all of the participants, there was a significant correlation between leptin and body mass index before pregnancy ($r = 0.416$, $p = 0.001$).

Conclusion: Our data showed that serum leptin level was higher in GDM and had a positive correlation with insulin resistance. Our findings suggest that high leptin levels might be a risk factor for GDM and IGT in pregnant women.

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Keywords: Gestational diabetes mellitus; Impaired glucose tolerance test; Leptin

Introduction

Disorders of glucose metabolism in pregnancy, such as gestational diabetes mellitus (GDM) and gestational impaired glucose tolerance (IGT), complicate pregnancy and these disorders are the main causes of adverse pregnancy outcomes [1]. Like all forms of hyperglycemia, GDM is characterized by insulin levels that are insufficient to meet insulin demands [2].

The pathogenesis of GDM has not been clearly explained. The most common theory is that GDM is caused by decreasing insulin sensitivity and increasing anti-insulin hormones that are secreted by the placenta during pregnancy, such as

human placental lactogen, prolactin, glucocorticoid, and progesterone [3].

New potential mediators of insulin resistance, including antiobesity hormone and leptin, have been recently investigated [4]. Leptin is an adipocyte-derived hormone, which is produced by some tissues, including the stomach, intestine, and the placenta in humans [4,5], and acts on the receptors of the hypothalamus to decrease food intake and increase energy consumption [5]. Some studies suggest that leptin also has a main effect on the regulation of whole body glucose homeostasis [6,7]. Some studies demonstrated a positive correlation between direct and indirect measures of adiposity with plasma leptin concentrations [8]. In pregnant women with changes in maternal fat stores and glucose metabolism, leptin increases [9]. Maternal leptin concentration increases 2–3 times above the nonpregnant concentration with the peak around 28 weeks of gestation [9]. Some clinical studies imply

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that increasing maternal plasma leptin may result from an upregulation of adipocyte leptin synthesis in the presence of increasing insulin resistance and hyperinsulinemia in the second half of pregnancy [10]. Researchers have illustrated that leptin directly affects whole body insulin sensitivity through regulating the efficiency of insulin-mediated glucose metabolism by skeletal muscle [11] and by hepatic regulation of gluconeogenesis [12]. The findings of some studies indicate that leptin has an acute inhibitory effect on secretion of insulin [6]. Large epidemiological studies have shown that plasma leptin concentrations were positively associated with insulin resistance in men and nonpregnant women [13].

In summary, available data suggest a complex relation between leptin and glucose homeostasis in humans. To our best knowledge, only two teams of investigators have studied maternal leptin concentrations in GDM women and the related published results are conflicting. On the other hand, the available data do not clarify whether the alterations in leptin concentrations are the cause or consequence of the metabolic disturbances, such as hyperglycemia, that are intrinsic to GDM. Additionally, the severity of any possible association of GDM risk with different concentrations of leptin was not assessed in either study [14,15]. We meant to explore the relationship of leptin concentration with insulin resistance in GDM.

Materials and methods

A case-control study was done at the Yazd Diabetes Research Center in 2007–2008 in Iran. In our study settings, all pregnant women were screened at 24–28 weeks of gestation using a 50 g glucose challenge test using Carpenter and Coustan criteria [16]. Those patients who have abnormal response accordingly (postload glucose concentrations of 130 mg/dL or higher) underwent a standard 100 g, 3-hour oral glucose tolerance test (OGTT). Women were diagnosed with GDM if at least two of four diagnostic criteria were met or exceeded [fasting plasma glucose (FPG) ≥ 95 mg/dL, for 1 hour, 2 hours, and 3 hours was ≥ 180 mg/dL, ≥ 155 mg/dL, ≥ 140 mg/dL, respectively]. Women with one abnormal OGTT value on the 3-hour OGTT were considered as having gestational IGT.

By consecutive patient selection, 29 women with GDM, 26 women with IGT, and 27 healthy pregnant women with normal OGTT were included in our study. Women with pre-GDM, chronic disease, and hypertension were excluded.

Normal pregnant women were matched with the GDM and IGT groups according to age, gestational age, and body mass index (BMI) before pregnancy.

The institution's Research Ethics Committee approval was obtained before study enrollment. All subjects gave written informed consent for participation in the study.

From their medical records, information was obtained, including maternal age, parity, gestational age, height, pre-pregnancy weight, reproductive and medical histories, and prepregnancy BMI (kilogram/meter square). These were entered in analysis of the data as covariates. Maternal height

and weight were measured by standard methods and BMI was calculated by dividing the weight in kilograms by the height in meters squared.

A blood test was done at 28 weeks of gestation. Maternal fasting plasma samples, collected in 10 mL vacutainer tubes, were frozen at -80°C .

Samples were thawed at room temperature, and then plasma glucose concentrations were measured in certified clinical laboratories using photometric method. The intra-assay coefficient of variation for glucose was 1.7% and interassay coefficient of variation was 1.1%. This assay had a sensitivity margin of 5 mg/dL.

Serum leptin concentrations were measured using a sensitive ELISA kit (Biosource Kap 2281, Denmark). The intra-assay coefficient of variation for the leptin was 4.4%. This assay had a sensitivity margin of 0.1 ng/mL.

Insulin concentrations were detected from serum using a human ELISA Kit (Biosource Kap 2281, Denmark). The intra-assay coefficient of variation for the insulin was 6.3% and the interassay coefficient of variation was 2%. This assay had a sensitivity margin of 1 $\mu\text{Iu/mL}$.

The insulin sensitivity index from the OGTT was calculated according to the homeostatic model assessment (HOMA) equation. HOMA is derived from the product of the FPG and the fasting plasma insulin (FPI) divided by a constant (22.5) [HOMA = (FPG \times FPI)/22.5] [17].

HOMA index values below 3.0 were considered as normal, whereas values equal to or above 3.0 indicated severe insulin resistance. All chemical analyses were done in the medical laboratory center of Yazd University.

All statistical analyses were performed by using SPSS for Windows, version 11.5 (SPSS, Inc., Chicago, IL, USA). Data of continuous variables were expressed as mean \pm standard deviation and many of our results did not have the normal distribution so the results were presented as median, minimum, and maximum values. For comparison of means of serum leptin between three groups, one-way analysis of variance was used; and for comparison of means of serum continuous variables between pairs of groups, the Bonferroni test was used. The insulin and HOMA index, which were not normally distributed, were compared using the Kruskal-Wallis test among the three groups.

For assessment of correlation between variables in the three groups Pearson correlation was used. Statistical significance was set at p value less than 0.05.

Results

Eighty-two pregnant women participated in this study, which included 29 women with GDM, 26 women with the IGT, and 27 healthy pregnant women with normal OGTT. The baseline characteristics of the pregnant women are shown in Table 1.

The serum leptin was significantly higher in women with GDM compared with the IGT and healthy pregnant women ($p = 0.03$) (Fig. 1). The difference of serum leptin between GDM versus the IGT group ($p = 0.1$) and the IGT versus

Table 1

The baseline characteristics of pregnant women who were screened for gestational diabetes mellitus

Baseline characteristics	GDM (<i>n</i> = 30) (mean ± SD)	IGT (<i>n</i> = 28) (mean ± SD)	Normal (<i>n</i> = 31) (mean ± SD)	<i>p</i> ^a
Age (yr)	27.9 ± 6.1	26.9 ± 5.3	27.3 ± 4.9	0.22
Parity (<i>n</i>)	2.2 ± 1.31	1.5 ± 1.15	2.2 ± 0.97	0.07
BMI (kg/m ²)	26.7 ± 3.7	25.7 ± 2.6	26.7 ± 4.5	0.31
Gestational age (wk)	25.6 ± 1.4	25.4 ± 0.9	26.1 ± 1.1	0.23

^a By one-way ANOVA.

ANOVA = analysis of variance; GDM = gestational diabetes mellitus; IGT = impaired glucose tolerance; SD = standard deviation.

control group (*p* = 0.2) were not statistically significant. In women with GDM, FPG, insulin, and HOMA index were higher than in the normal group (Table 2).

In all of the participants, there was a significant correlation between leptin and BMI before pregnancy (*r* = 0.416, *p* = 0.001) and insulin levels (*r* = 0.221, *p* = 0.04). There was a positive correlation between leptin, insulin, and HOMA index in GDM (*r* = 0.221, *p* = 0.03), (*r* = 0.246, *p* = 0.03).

Leptin had a negative correlation with age and parity (*r* = −0.04, *p* = 0.72), (*r* = −0.103, *p* = 0.38), and a positive correlation with gestational age (*r* = 0.219, *p* = 0.06), but these correlations were not significant. We used the odds ratio to establish the cutoff point for leptin level and a receiver operating characteristic curve was drawn. Leptin level ≥20.5 ng/mL could be a predictor for the risk of GDM (sensitivity 80%, specificity 50%) (Fig. 2).

Discussion

Women with GDM had higher serum leptin concentrations than IGT and non-GDM women. Our results are generally consistent with studies that assessed maternal plasma leptin

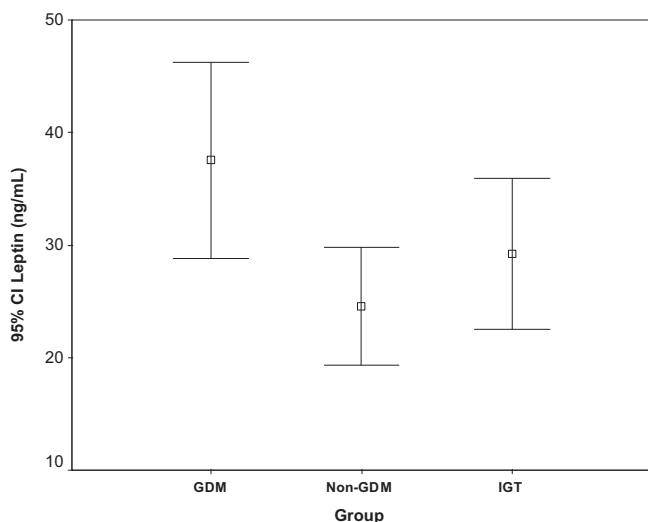


Fig. 1. Comparison between the mean of leptin (ng/mL) in pregnant women with GDM, IGT, and normal glucose homeostasis. CI = confidence interval; GDM = gestational diabetes mellitus; IGT = impaired glucose tolerance.

Table 2

Mean (SD) or median (interquartile range) of leptin, fasting blood sugar, insulin concentrations, and HOMA index in pregnant women with GDM, IGT, and normal glucose homeostasis

Parameters	GDM (<i>n</i> = 30)	IGT (<i>n</i> = 28)	Normal (<i>n</i> = 31)	<i>p</i>
Leptin (ng/mL) ^{a,b}	30.60 (33.40)	24.10 (17.07)	21.60 (12.60)	0.03
Insulin (IU/mL) ^c	26.84 ± 5.3	20.7 ± 3.6	11.8 ± 4.9	0.04
HOMA index ^c	6.68 ± 1.3	5.1 ± 1.07	2.3 ± 0.9	0.04
Fasting blood sugar (mg/dL) ^{c,d}	98.7 ± 14.78	97 ± 7.29	83 ± 23.6	0.07

^a Women with GDM versus normal group (*p* < 0.05).

^b Median/interquartile range.

^c Mean ± SD.

^d Women with IGT versus normal group (*p* < 0.05).

GDM = gestational diabetes mellitus; HOMA = homeostatic model assessment; IGT = impaired glucose tolerance; SD = standard deviation.

concentrations in pregnancies complicated by GDM. In a case-control study, Kautzky-Willer et al [15] reported that maternal third-trimester plasma leptin concentrations were higher in GDM women compared with the control group (24.9 ng/mL vs. 18.2 ng/mL; *p* = 0.001). Such a relation was also found in the Vitoratus et al [18] and Qiu et al [19] studies. Liu et al [20] showed that serum leptin level is correlated with glucose tolerance during pregnancy.

However, Festa et al [14], in an earlier case-control study, noted that maternal third-trimester leptin concentrations were significantly lower in GDM cases as compared with controls after adjusting for possible confounding factors, such as BMI and insulin concentrations. Several possible explanations are suggested for the disparities in the existing studies. The study

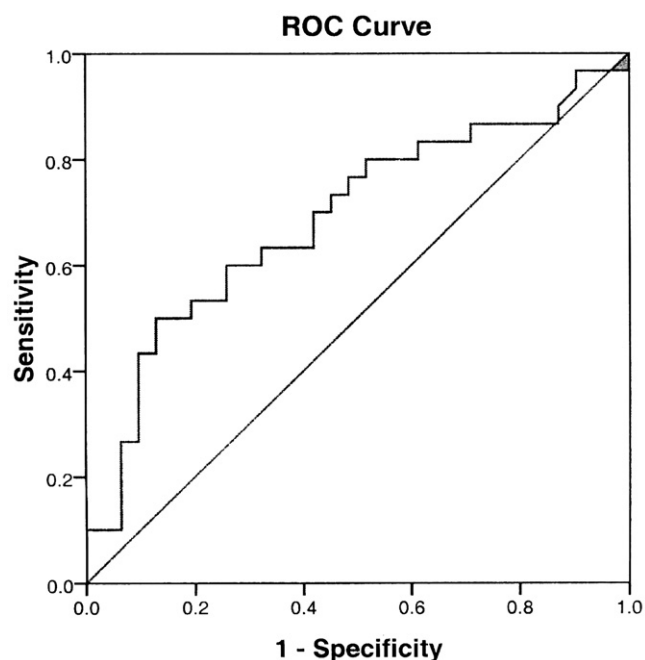


Fig. 2. ROC curve of threshold leptin levels for predicting GDM. Serum leptin level ≥20.5 ng/mL could be the predictor threshold point for GDM (sensitivity 80%, specificity 50%). GDM = gestational diabetes mellitus; ROC = receiver operating characteristic.

design and the confounding factors, such as the time of blood sampling (whether blood samples were collected before, after, or during labor) and maternal factors, including whether women were treated with medication or diet before blood was collected for leptin determination, might account for differences. Moreover, variations in population characteristics and status of glycemic control could also account for some of the observed differences in study results. An important limitation of the two available studies is the design of those studies in which leptin concentrations were determined after the diagnosis of GDM. In this case, it cannot be determined whether any observed alterations in plasma leptin concentrations preceded GDM or whether the differences might be attributed to disease-related alterations in glucose metabolism [19].

In a nested case-control study by Gao et al [3], 22 women with GDM, 10 with IGT, and 20 healthy pregnant women were chosen from the women who had visited at 14–20 weeks of gestation and had blood samples prospectively taken and kept during their visit. Findings of this study showed that women with GDM have the highest values of leptin compared with those with IGT and the healthy controls at 14–20 weeks of gestation.

Some studies evaluated the relationship between leptin concentration and insulin resistance. Maghbooli et al [21] found that leptin concentration was positively associated with insulin level and HOMA index. Liu et al [20] showed a positive and significant correlation between the maternal leptin and fasting insulin levels. Our results indicate that plasma insulin levels are higher in GDM and IGT compared with the normal group, and the serum leptin had a significant positive correlation with insulin and HOMA index.

However, Mohiti et al [22] reported that the serum leptin had a negative correlation with insulin in obese diabetic patients.

Our findings are consistent with a much larger body of evidence from experimental, clinical, and epidemiological investigations, which suggest that leptin is an important mediator of glucose homeostasis in humans and plasma leptin has a significant positive correlation with BMI. Liu et al [20] also has shown that leptin predicts the development of GDM independent of maternal BMI and other risk factors. The findings of this prospective study are generally consistent with the reports by Kautzky-Willer et al [15], Lappas et al [23] and Qiu et al [19], as well.

Our finding showed that the predicting threshold for GDM was serum leptin levels ≥ 20.5 ng/mL, but as the area under the curve is less than 80%, this threshold is not the best predicting point for leptin in GDM women. So, we need a prospective study in larger population of GDM women.

In conclusion, we found that patients with GDM had higher serum leptin levels than IGT and non-GDM women, and women with higher BMI had a higher level of leptin concentration. These results show the presence of an association between serum leptin level and glucose metabolism in GDM. As to whether the high leptin levels can serve as a predictive factor for GDM development, larger prospective studies are needed to address this issue.

Acknowledgments

The authors would like to thank Mr. Attar and Mrs. Razm-ara, employees of Yazd Blood Transfusion Organization, for blood sampling.

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