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Relationship of leptin with insulin indices in gestational diabetes mellitus

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Abstract

Background: Leptin is thought to increase and affect glucose and insulin homeostasis in gestational diabetes mellitus (GDM).

Objectives: To see the relationships among leptin, insulin indices (homeostatic model of insulin assessment, HOMA-IR), and obesity among women with GDM.

Methods: Women (n=107) with 24-28 weeks gestation were tested by 75 gm oral glucose (OGTT) to divide into GDM [n=45, age: 27.80±3.98 years, mean±SD; BMI: 27.88(24.46, 30.43) kg/m^2, median] and normal glucose tolerance [NGT; n=62, age: 26.19±5.30 years, mean±SD; BMI: 25.80(23.65,28.42) kg/m^2, median] following WHO-2013 diagnostic criteria. Fasting plasma glucose, insulin, and leptin were measured by glucose oxidase and ELISA methods respectively.

Results: Glucose values (fasting, 01h, and 02h; mmol/L) were significantly higher in GDM than those of NGT in both subgroups of HOMA-IR [≥2.89: insulin resistant (IR), <2.89: insulin sensitive (IS)]. BMI was significantly higher in GDM with IR than that of GDM with IS whereas fasting insulin in both the HOMA-IR subgroups of GDM as well as of NGT differed significantly. None of the BMI nor glucose values of OGTT or fasting insulin correlated significantly with leptin either in GDM or in NGT in the subgroup with IR; whereas in the IS-subgroup, BMI, 01hG, 02hG, and fasting insulin correlated significantly in NGT only. ROC curve analysis for leptin revealed it as an unreliable marker of IR (AUC = 0.553) in GDM.

Conclusions: Serum leptin does not correlate with insulin indices in GDM. *[J Assoc Clin Endocrinol Diabetol Bangladesh, July 2023; 2 (2):46-51]*

Keywords: Insulin indices, leptin, gestational diabetes mellitus, insulin resistance

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Introduction

The prevalence of gestational diabetes mellitus (GDM) is observed increasing globally. It develops as an outcome of discordance between insulin resistance (IR) and secretary capacity; perhaps because of the contribution of pre-existing IR, or because of inadequate β-cell expansion and concomitant insulin insufficiency.[1] This is accentuated by obesity and overweight-related factors like chronic subclinical inflammation and low-grade activation of the acute phase response.[2,3] Adipocyte-derived hormones "adipocytokines" and their role in the regulation of maternal metabolism, gestational IR, and β-cell dysfunction have opened a new era in understanding the pathophysiology of GDM. Among adipocytokines, leptin is thought to be a new potential mediator of IR during pregnancy.[4] During pregnancy, with increasing fat deposition and mobilization circulating leptin level also increases.[5] However, leptin gene expression is significantly increased both in the placenta and visceral adipose tissue in GDM compared with pregnancy with normal glucose tolerance (NGT).[6,7] On the other hand, gestation is a state of both central and peripheral resistance to leptin especially during mid-pregnancy which allows the anabolic metabolism in the mother.[8] As a result, leptin level rises to 2–3 fold higher than the nonpregnant state with a peak at around 24-28 weeks of gestation, plateaus thereafter, and declines slightly before delivery and falls at postpartum.[6] This hyperleptinaemia contributes to enhanced IR and by overruling the leptin-induced suppression of insulin secretion from β-cells eventually amplifies hyperinsulinemia which sequentially results in

glucose intolerance. Leptin also inhibits insulin biosynthesis and secretion from pancreatic β-cells through leptin receptors in pancreatic β-cells.[9] In contrast, insulin stimulates leptin secretion from adipose tissue and thus makes a hormonal regulatory feedback loop of the existing adiponectin-insulin axis. Recently, several studies have focused on leptin, as a potential mediator of IR in pregnancy.[10,11] But the results are variable and in some cases contradictory too. Some reported a positive correlation between leptin, insulin, and insulin indices in GDM whereas; others found no correlation between IR and leptin.[10,12] The aim of this study was to determine the circulating level of leptin and its relation with insulin and different insulin indices in women with GDM and those who are normal for glucose tolerance (NGT).

Methods

This cross-sectional study was performed at the Department of Endocrinology of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. Pregnant women at 24-28 weeks of gestation attending the 'Antenatal Clinic' of Obstetrics and Gynecology, BSMMU who fulfilled the inclusion and exclusion criteria, were referred to 'The GDM Clinic' of the Department of Endocrinology, BSMMU. They were screened and enrolled consecutively from March 2019 to August 2020. A 75 gm three samples oral glucose tolerance test (OGTT) was performed after an overnight fast according to WHO guidelines-2013, to divide them into GDM and NGT. Thus, 45 GDM and 62 pregnant women with NGT were enrolled in the study. The Institutional Review Board (IRB) duly approved the protocol before enrollment, and all participants provided written informed consent. Data were collected in a prescribed data sheet. Patients with overt DM, DM in pregnancy, or any acute or chronic medical condition were excluded from the study. Fasting samples for leptin and insulin were collected on the day of OGTT; after clot formation serum separated and preserved under -70^{o}C freezer until assay. Glucose was measured on the same day within two hours of sampling.

Blood glucose was measured by glucose oxidase method using Dimension EXL 200 Integrated Chemistry System (Siemens, Germany) whereas leptin by enzyme-linked immunosorbent assay (ELISA) using DRG Leptin (Sandwich) ELISA kit (EIA-2395), Inc. USA. Intra-assay CV for glucose was for low level 1.73% and for high level 4.22%. Leptin was measured in a single run-assay and intra-assay CV for leptin was 4.9%. Insulin was measured by chemiluminescent microparticle immunoassay. Insulin indices were calculated by the homeostasis model assessment (HOMA) method. HOMA-IR cut-off of 2.89 was considered to categorize the study participants as IR or insulin sensitive (IS).[13]

All data were processed by using the IBM SPSS software program (version 25.0) and expressed as frequencies (percentages) for qualitative values and median with interquartile range (25th -75th percentile) for quantitative data. The chi-square test (for qualitative) and Mann-Whitney U test (for quantitative) were done to compare between groups. The correlation of leptin with clinical and biochemical variables was analyzed by Spearman's correlation test. Receiver operating characteristics (ROC) curve analysis was done to see leptin as a marker of IR in GDM patients. P-values <0.05 were considered statistically significant.

Results

Among 45 GDM mothers, 13 had IR and among 62 NGT mothers, five had IR. BMI and systolic BP were significantly higher in the IR group than IS group in GDM mothers only. Serum leptin was statistically similar between GDM and NGT [26.05(16.92, 50.55) vs. 23.50(14.95, 38.30) median, p=0.360]. Fasting glucose (FG), 01-hour OGTT-glucose (01hrG), 02-hour OGTT-glucose (02hrG) median values were all significantly higher in GDM than those of NGT in both the subgroups of HOMA-IR [GDM vs. NGT: FG (5.60 vs. 4.70, p <0.001); 01hrG (9.80 vs. 7.0, p <0.001); 02hrG (7.54 vs. 6.10, p <0.001), mmol/L]. Unlike glucose, median fasting insulin was significantly higher in GDM than NGT in the IR group (16.41 vs. 14.70, μIU/ml, p=0.012) but not in the subgroup of IS (7.05 vs. 6.25, μIU/ml, p=0.135). Median BMI was significantly higher in GDM with IR than that of GDM with IS (29.52 vs. 26.68, kg/m^2, p=0.016) whereas median fasting insulin in those two HOMA-IR subgroups of GDM (16.41 vs. 7.05, μIU/ml, p<0.001) as well as of NGT (14.70 vs. 6.25, μIU/ml, p<0.001) differed significantly (Table-I).

None of age, gestational age, BMI, and glucose value of OGTT or fasting insulin correlated significantly with leptin either in GDM (NS for all) or in NGT (NS for all) in the subgroup with IR (Table-II) whereas in the subgroup with IS, BMI (p<0.001), 01hG (p=0.047), 02hG (p=0.029) and fasting insulin (p=0.019) correlated significantly in NGT only but not in GDM (Table-III).

Table-I: Characteristics of the study population with insulin resistance (n=107)

Variables	Insulin resistant (HOMA-IR ≥2.89)			Insulin sensitive (HOMA-IR <2.89)			GDM	NGT
	GDM (1)	NGT (2)	p	GDM (3)	NGT (4)	p	(1) vs. (3)	(2) vs. (4)
No.	13	5		32	57		p	p
Age, years	30.0 (26.0-30.5)	26.0 (22.50- 31.50)	0.396	28.0 (24.0-30.0)	25.0 (22.0-30.0)	0.097	0.568	0.752
Gestational age, weeks	26.0 (24.0, 27.50)	24.0 (24.0-26.50)	0.524	27.0 (25.25-28.0)	26.50 (24.0-28.0)	0.514	0.165	0.147
BMI, kg/m^2	29.52 (27.55-35.12)	28.54 (25.18-30.44)	0.402	26.68 (22.72-29.37)	25.77 (23.43-28.21)	0.588	**0.016**	0.207
Systolic BP, mm-Hg	120.0 (100.0-120.0)	110.0 (100.0-120.0)	0.400	100.0 (100.0-110.0)	100.0 (100.0-110.0)	0.458	**0.036**	0.218
Diastolic BP, mm-Hg	70.0 (65.0-80.0)	70.0 (70.0-75.0)	0.957	70.0 (70.0-77.50)	70.0 (60.0-70.0)	0.104	0.515	0.169
Fasting glucose, mmol/L	5.60 (5.30-5.90)	4.70 (4.20-4.85)	**0.001**	5.20 (4.95-5.83)	4.50 (4.20-4.68)	**<0.001**	0.065	0.452
1-H OGTT glucose, mmol/L	9.80 (8.80-10.65)	7.0 (6.45-7.65)	**0.001**	9.90 (9.15-10.20)	7.60 (6.80-8.30)	**<0.001**	0.920	0.216
2H-OGTT glucose, mmol/L	8.70 (7.85-9.30)	6.50 (5.75-7.40)	**0.014**	7.54 (6.83-8.98)	6.10 (5.40-7.14)	**<0.001**	0.077	0.502
Fasting insulin, µIU/mL	16.41 (15.55-19.80)	14.70 (12.48-15.30)	**0.012**	7.05 (4.42-8.56)	6.25 (4.03-7.73)	0.135	**<0.001**	**<0.001**
Fasting leptin, ng/mL	26.80 (18.60-51.10)	25.10 (21.80-44.95)	0.961	23.10 (12.93-39.63)	22.65 (14.53-38.40)	0.788	0.515	0.408

Data were expressed in median (IQR), Mann Whitney U test was done

Table-II: Correlations of serum leptin with different variables under subgroups of insulin resistance (n=18)

Determinants of 'r'	GDM		NGT	
	r	p	r	p
Age, years	-0.330	0.271	-0.700	0.188
Gestational age, weeks	-0.076	0.805	-0.112	0.858
BMI, kg/m^2	0.206	0.499	-0.600	0.285
Systolic BP, mm-Hg	0.094	0.760	0.632	0.252
Diastolic BP, mm-Hg	0.221	0.468	0.001	1.00
Fasting glucose, mmol/L	-0.149	0.626	-0.410	0.493
1-H OGTT glucose, mmol/L	-0.315	0.295	0.001	1.00
2H-OGTT glucose, mmol/L	-0.380	0.201	-0.100	0.873
Fasting insulin, µIU/mL	0.286	0.343	0.300	0.624

Spearman's correlation test was done

Table-III: Correlations of serum leptin with different variables under subgroups of insulin sensitivity (n=89)

Determinants of 'r'	GDM		NGT	
	r	p	r	p
Age, years	0.144	0.433	0.226	0.095
Gestational age, weeks	0.143	0.436	-0.063	0.643
BMI, kg/m^2	0.268	0.138	0.540	**<0.001**
Systolic BP, mm-Hg	0.143	0.435	0.152	0.264
Diastolic BP, mm-Hg	0.077	0.675	0.190	0.161
Fasting glucose, mmol/L	0.320	0.075	0.151	0.265
1-H OGTT glucose, mmol/L	0.153	0.404	0.267	**0.047**
2H-OGTT glucose, mmol/L	0.210	0.249	0.293	**0.029**
Fasting insulin, µIU/mL	0.233	0.199	0.311	**0.019**

Spearman's correlation test was done

ROC curve analysis for leptin revealed area under the curve (AUC) for IR was 0.553 (p=0.515) suggesting it could not be used as a marker of IR in GDM (Figure-1).

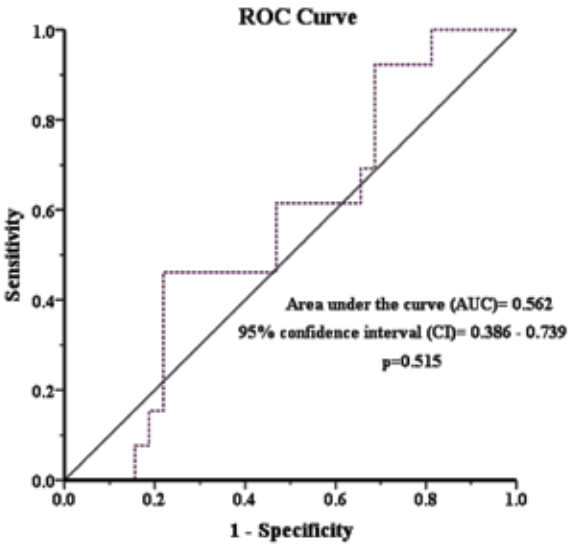

Figure-1: Leptin as a marker of insulin resistance (HOMA-IR ≥2.89) in GDM mothers (n= 45)

Discussion

In this study, we found that leptin had no significant associations with any studied clinical or biochemical parameters including BMI, glucose values, and insulin indices in GDM mothers irrespective of insulin status. Similarly, leptin had no significant associations with any studied variables in pregnant mothers with IR irrespective of glycemic status. Leptin was observed not to be an acceptable marker of IR in GDM. However, leptin had a significant association with BMI, OGTT glucose, and insulin in NGT mothers, especially in IS-NGT mothers.

Leptin was found little higher in GDM than in NGT mothers irrespective of insulin status. Similarly, leptin was found a little higher in IR than in IS mothers irrespective of glycemic status. However, none of the associations were statistically significant. Similarly, there were positive and significant correlations of leptin with BMI, glucose values, and insulin only in IS-NGT mothers but not in IR-NGT mothers or GDM mothers irrespective of insulin status. From these findings, it appears that the association of leptin with BMI, glucose values, or insulin indices is lost in women developing higher glucose and IR, alone or both during pregnancy. Similar findings are observed by Skvarca et al.[14] So, it is possible that upregulation of several inflammatory cytokines and acute phase proteins like tumor necrosis factor-α, interleukins (IL-6, IL-8) and high sensitivity C-reactive protein which may contribute to increasing IR but fails to maintain any similar influence on leptin which was not investigated in the present study.

Increased expression of soluble receptors rather than transmembrane receptors for leptin in the placenta may modulate leptin release from the placenta.[15] Higher expression of soluble receptors may reduce the risk of GDM development.[16] Besides, the placenta may play more role than adipose tissue in maternal leptin concentration and under different regulation than leptin from adipose tissue.[17] So it is possible that the IR related to adipose tissue may not be related to leptin secreted from the placenta.

Gao et al. found elevated leptin in GDM in correlation with HOMA-IR. However, the significance was lost when it was adjusted for BMI.[18] On the other hand, a systematic review and meta-analysis found elevated leptin in GDM mothers when compared with BMI-matched NGT mothers.[19] We also found a positive correlation of serum leptin with BMI in all pregnant women irrespective of glycemic status.[20] These findings also suggest that the association of leptin is better with BMI rather than glycemic status or its causative factor(s) like IR or deficient β-cells' function. Apropos with this, some studies also found that leptin level is higher before pregnancy with little elevation during pregnancy in fasting as well as after OGTT and remains elevated even after pregnancy in GDM mothers than in NGT mothers.[11,21] Therefore, it seems pertinent to assume that leptin is unlikely to have any predictive value over GDM.

There are some limitations of our study. The sample size was small. We have no pre-pregnancy data on BMI and leptin levels. A study on leptin levels in all the trimesters of pregnancy as well as before conception and after parturition that is a longitudinal study may provide more insights into the association of leptin with IR and glycemic status in GDM patients.

Conclusions

We would like to conclude that serum leptin has no significant association with insulin indices in GDM and leptin is not sufficiently sensitive to replace HOMA–IR for predicting GDM. However, it is too early to infer the interaction and role of leptin in the event of the development of GDM. A comprehensive study encompassing other adipokines and cytokines and probable genetic and environmental risk factors may highlight a clearer view of this avenue. Our group is investigating the importance of other cytokines in GDM during the period of 24-28 weeks of gestation (the

optimum time for GDM screening) to be reported subsequently.

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Conflict of Interest

The authors have no conflicts of interest to disclose.

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Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Ethical approval for the study was obtained from the Institutional Review Board, BSMMU (No. BSMMU/2019/3861, Date: 11/04/2019). The written informed consent was obtained from all study participants. All methods were performed in accordance with the relevant guidelines and regulations.

Author's contributions

Conceptualization (CAM, SJ, MAH), Methodology (CAM, AAS, MAH), Formal analysis (CAM, MSM), Investigation (CAM, SP, TT), Data curation (CAM), Original draft preparation (CAM, MSM), Review & editing (SJ, AAS, MAH), Visualization (CAM, MSM), Supervision, Project administration & Funding acquisition (SJ, AAS, MAH)

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