Scientific Research Publishing

Journal of Biosciences and Medicines, 2020, 8, 44-54
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Insulin Sensitivity and Insulin Secretion Estimated by Homeostatic Model Assessment (HOMA) in Gestational Diabetes Mellitus

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How to cite this paper: Mahjabeen, S., Rahman, A.K.M.S., Hossain, M., Mustari, M., Abedin, M., Mahmood, T., Chowdhury, T.I., Islam, T. and Hossain, R.M. (2020) Insulin Sensitivity and Insulin Secretion Estimated by Homeostatic Model Assessment (HOMA) in Gestational Diabetes Mellitus. *Journal of Biosciences and Medicines*, **8**, 44-54.
https://doi.org/10.4236/jbm.2020.87005

Received: June 19, 2020
Accepted: July 18, 2020
Published: July 21, 2020

Abstract

Background: Progressive insulin resistance (IR) is an important pathophysiologic mechanism of gestational diabetes mellitus (GDM). Homeostatic model assessment (HOMA) is commonly used as a parameter of the severity of insulin resistance. **Aims:** To determine indices of insulin resistance (IR) and β-cell function in gestational diabetes mellitus (GDM). **Methods:** This cross sectional study was conducted from March 2017 to September 2018 at Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. The study was performed with 41 GDM and equal number of pregnant women with normal glucose tolerance (NGT) diagnosed on basis of WHO criterion-2013 during 24 - 40 weeks of gestation. Serum glucose was measured by glucose oxidase method and fasting serum insulin was measured by chemiluminescent immunoassay. Equations of homeostatic model assessment (HOMA) were used to calculate insulin indices like-insulin resistance (HOMA-IR), β-cell function (HOMA-B) and insulin sensitivity (HOMA-%S). Data were analyzed and compared by statistical tests. **Results:** A total of eighty-two (82) subjects [41 women with GDM (age: 28.29 ± 3.79 years, BMI: 27.16 ± 4.13 kg/m^2) and 41 women with NGT (age: 26.22 ± 5.13 years, BMI: 25.27 ± 3.01 kg/m^2)] were included in this study. It was observed that GDM women were significantly older ($p = 0.041$) and had significantly higher BMI ($p = 0.020$) than pregnant women with NGT. The

GDM group had significantly higher IR as indicated by higher fasting insulin value [GDM vs. NGT; 10.19 (7.71 - 13.34) vs. 6.88 (5.88 - 8.47) μIU/ml, median (IQR); $p = 0.001$] and HOMA-IR [GDM vs. NGT; 2.31 (1.73 - 3.15) vs. 1.42 (1.15 - 1.76), median (IQR); $p < 0.001$], poor β-cell secretory capacity [GDM vs. NGT; HOMA-B: 112.63 (83.52 - 143.93) vs. 128.60 (108.77 - 157.58), median (IQR); $p = 0.04$] and low insulin sensitivity [GDM vs. NGT; HOMA-%S: 43.29 (31.77 - 57.98) vs. 70.42 (56.86 - 86.59), median (IQR); $p < 0.001$]. **Conclusions:** GDM is associated with both insulin resistance and inadequate insulin secretion.

Keywords

Gestational Diabetes Mellitus (GDM), Homeostatic Model Assessment (HOMA), Insulin Resistance (IR), Normal Glucose Tolerance (NGT)

1. Introduction

Pregnancy is a state of physiological insulin resistance (IR). The development of the fetal-placental unit during pregnancy causes endocrine changes that trigger a shift in maternal nutrient metabolism. Estradiol increases insulin binding. Progesterone, cortisol, human placental growth hormone and human placental lactogen induce insulin resistance each on their own way. The increased resistance is caused by the cellular effects of the increased levels of one or all of the above hormones [1] [2]. For normal glucose homeostasis to be maintained in pregnancy, the β-cell must compensate for this IR by increasing the secretion of insulin [3]. An insufficient compensatory response will result in maternal hyperglycemia, as occur in the setting of gestational diabetes mellitus (GDM).

GDM develops as a consequence of either unusually high IR, perhaps because of contribution of pre-existing IR in overweight women, or because of inadequate β-cell expansion and concomitant insulin insufficiency [4]. Studies performed so far have indicated the presence of pancreatic β-cell dysfunction in GDM which makes it difficult for insulin to be secreted in relation to glycaemia and the severity of IR [5]. In Asians, the pancreatic β-cell mass is relatively smaller than the Westerners, and the insulin secretory capacity is also lower [6]. Moreover, β-cell adaptation during pregnancy was significantly lower in South Asian pregnant women compared with Western Europeans [7]. Women with a history of GDM, who become glucose tolerant at postpartum, still continue to have high IR and β-cell dysfunction, whereas non-GDM women exhibit a marked fall in IR [8]. This persistence of decreased β-cell function in a background of raised IR increases their susceptibility to future diabetes. That is why GDM is well known to be an antecedent of type 2 diabetes [9].

Among various indices for the measurement of insulin sensitivity/resistance, the hyperinsulinemic-euglycemic clamp index is the gold standard. But it is expensive and impractical for routine use. Currently, the homeostasis model as-

sessment (HOMA) model, which correlates well with gold standard clamp techniques, is widely used in research because of its simplicity. The HOMA model was first described in 1985 by Matthews *et al.* and has been used in many clinical and epidemiological studies to derive β-cell function and IR values from fasting plasma insulin and glucose [10] [11]. HOMA is a model of the relationship of glucose and insulin dynamics that predicts fasting steady-state glucose and insulin concentrations for a wide range of possible combinations of IR and β-cell function. The HOMA of insulin resistance (HOMA-IR) index is regarded as a simple, inexpensive, and reliable measure of insulin resistance. On the other hand, HOMA of β-cell function (HOMA-B) index is a good measure of β-cell function [12]. Estimates of β-cell function using HOMA-B have been shown to correlate well with estimates using continuous infusion glucose model assessment (CIGMA), hyperglycemic clamp and the acute insulin response from the intravenous glucose tolerance test (IVGTT) [13]. HOMA-IR is an accurate index of insulin sensitivity throughout pregnancy in women with GDM and it correlates well with the severity and pathophysiological heterogeneity of GDM [14]. In a previous study, women with HOMA-IR values > 2.89 required early insulin therapy and daily insulin dose exhibits strong correlation with HOMA-IR index values [14]. HOMA-IR values measured in first trimester were higher (>2.60) in women who were subsequently diagnosed as GDM with the results of the second-trimester glucose tolerance test [15]. Low HOMA-B indices in GDM women were found to be related to postpartum diabetes at 5 years follow-up in another study [16]. Researchers already revealed poorer HOMA-B index in GDM women of South Asia [6] [7]. So, these HOMA indices can be potential markers for the personalization of therapy in GDM patients, thus helpful in optimizing GDM management as well as in preventing future complications.

This study was intended to examine the differences in the insulin sensitivity and secretion indices between GDM and pregnant women with NGT. Results of the study might hopefully contribute to the understanding of pathophysiology of GDM.

2. Materials and Methods

2.1. Study Design

This cross-sectional study was conducted at Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from March 2017 to September 2018 to examine the differences in insulin indices between GDM and pregnant women with NGT. The study was approved by the Ethical Review Committee, BSMMU, Dhaka, Bangladesh. According to the statistical calculation, a total of eighty-two (82) study subjects [41 GDM women, diagnosed by the WHO 2013 criteria as cases and 41 healthy pregnant women (NGT) as control subjects] were included in this study. The differences in insulin indices between the groups were analyzed and compared.

2.2. Sample Size Estimation

In a previous study, HOMA IR was 3.8 ± 3.05 (mean ± SD) in GDM group and 1.79 ± 1.08 in pregnant women with NGT [17].

Sample size [18] for each group,

$$n = \left[\left(z_\alpha + z_\beta \right)^2 \times \left(\sigma_1^2 + \sigma_2^2 \right) \right] \Big/ \left(\mu_1 - \mu_2 \right)^2$$

where,

z_α = z-value of standard normal distribution at 5% level of significance = 1.96;

z_β = z-value of standard normal distribution at 95% power = 1.64;

σ_1 = standard deviation in GDM group = 3.05;

σ_2 = standard deviation in pregnant women with NGT group = 1.08;

μ_1 = mean in GDM group = 3.8;

μ_2 = mean in pregnant women with NGT group = 1.79.

So,

$$\begin{aligned} n &= \left[\left(1.96 + 1.64 \right)^2 \times \left\{ \left(3.05 \right)^2 + \left(1.08 \right)^2 \right\} \right] \div \left(3.8 - 1.79 \right)^2 \\ &= \left(12.96 \times 10.47 \right) \div 4.04 \\ &= 135.69 \div 4.04 \\ &= 33.5866 \\ &= 34 \left(\text{approximately} \right) \end{aligned}$$

In this study, 41 GDM patients and equal number of pregnant women with NGT were recruited according to feasibility.

2.3. Subjects

This study encompassed 41 women with GDM and equal number of pregnant women with NGT screened by 3-samples of OGTT following WHO 2013 criterion for GDM. Women after 24 weeks of gestation with singleton pregnancy attending at department of Endocrinology BSMMU during the study period were screened and enrolled consecutively. Pregnant women with overt diabetes, diabetes mellitus in pregnancy (DIP) and subjects with other co-morbid diseases (hepatic, renal or thyroid disorders, chronic infections etc.) were excluded from the study.

2.4. Recruitment of the Subjects

After taking brief history, preliminary selection was done, and the purpose of the study was explained in details to each subject and their verbal consent was taken. They were advised to take unrestricted carbohydrate diet, to do normal physical activities and to avoid all vitamin supplementations for 3 days. Then they were requested to report in the Biochemistry laboratory, BSMMU after 3 days at morning between 8.00 - 10.00 am following an overnight (8 - 12 hours) fasting. When the subjects reported, after taking informed written consent their oral glucose tolerance test (OGTT) was done accordingly. Depending on the results of OGTT, study subjects were enrolled as GDM (fulfilling the WHO 2013 diag-

nostic criteria for GDM, which requires at least one of the following on the OGTT: fasting plasma glucose 5.1 - 6.9 mmol/L, 1-hour glucose ≥ 10.0 mmol/L, 2-hour glucose 8.5 - 11.0 mmol/L) [19]. Healthy pregnant women with normal OGTT (NGT) served as control subjects. Demographic data and anthropometric measurements as well as relevant other information of all study subjects were recorded in a data collection sheet.

2.5. Collection of Blood Samples

An overnight fasting (8 - 12 hours) blood sample was collected between 8.00 - 10.00 am from each subject. Venous blood (6 ml) was obtained by venipuncture following standard procedure. Subjects were then allowed to drink glucose water (75 gm glucose in 300 ml of water). Then they were requested not to take any food & beverage and be rested for next two hours. After 1 hour and 2 hours of glucose intake, the second and third blood samples (3 ml venous blood) were taken respectively following the same procedure.

2.6. Analysis of Blood Samples

Fasting (3 ml) and postprandial (3 ml) blood samples were taken into plain tubes (6 cc), while fasting venous blood (3 ml) for insulin were collected from each subject during OGTT in clot activator vacutainer tubes, then all blood samples were kept in room temperature in vertical position for 15 - 20 minutes. Serum was separated by centrifugation (around 8000 rpm) for 10 minutes in room temperature (22˚C - 24˚C) and preserved at −80˚C until further analysis.

2.7. Analytic Method

Plasma glucose was analyzed by glucose oxidase method by using Dimension EXL 200 Integrated Chemistry System (Siemens, Germany) on the same day of collection. Serum insulin level was measured by chemiluminescent immunoassay method using Access Immunoassay System (REF-33410), Beckman Coulter, Inc., USA. All biochemical tests of the study subjects were performed at the Biochemistry and Molecular Biology Laboratory, Department of Biochemistry and Molecular Biology, BSMMU, Dhaka, Bangladesh.

2.8. Assessment of Insulin Secretion and Sensitivity Index

Insulin resistance ((HOMA-IR), insulin secretion (HOMA-B) and insulin sensitivity (HOMA-%S) were evaluated using the equations of original HOMA model described by Matthews *et al.* [10].

1) HOMA of insulin resistance (HOMA-IR) index
   HOMA-IR = [Fasting insulin (μIU/ml) × Fasting glucose (mmol/ml)]/22.5
2) HOMA of β-cell function (HOMA-B) index
   HOMA-B = 20 × Fasting insulin (μIU/ml)/Fasting glucose (mmol/L) − 3.5
3) HOMA of insulin sensitivity (HOMA-%S) index
   HOMA-%S = (1/HOMA-IR) × 100%

A cut-off of HOMA-IR ≥ 2.89 was used to define high IR according to previous studies [14].

2.9. Statistical Analysis

All data were analyzed using the Statistical Package for Social Science (SPSS) software for Windows version-23. Results were expressed as frequencies or percentages for qualitative values and mean (± SD) for quantitative values. When quantitative values with skewed distribution were found, they were presented as median and inter quartile range (25^{th} - 75^{th} percentile). Comparison between subgroups was done by Chi-square test, unpaired Student's "t" test or Mann-Whitney U test as applicable. A p-value ≤ 0.05 was considered as statistically significant.

3. Results

To determine indices of insulin resistance (IR) and β-cell function in GDM and pregnant women with NGT, a total of eighty-two (82) subjects (41 GDM women, diagnosed by the WHO 2013 criteria as cases and 41 healthy pregnant women with NGT as control subjects) were evaluated. It was observed that women in the GDM group were significantly older (GDM vs. NGT: 28.29 ± 3.79 vs. 26.22 ± 5.13 years, mean ± SD; p = 0.041) and had significantly higher BMI (GDM vs. NGT: 27.16 ± 4.13 vs. 25.27 ± 3.01 kg/m^2, mean ± SD; p = 0.020) than pregnant women with NGT. However, none of the clinical parameters like gestational weeks, systolic and diastolic blood pressure, previous bad obstetric history [like-macrosomia, abortion, intra uterine death (IUD), abortion + IUD], family history of DM in 1^{st} degree relatives or previous history of GDM were statistically different between the two groups (p > 0.05) (Table 1).

The GDM group had significantly higher IR as indicated by higher fasting insulin value [GDM vs. NGT; 10.19 (7.71 - 13.34) vs. 6.88 (5.88 - 8.47) μIU/ml, median (IQR); p = 0.001] and HOMA-IR [GDM vs. NGT; 2.31 (1.73 - 3.15) vs. 1.42 (1.15 - 1.76), median (IQR); p < 0.001], poor β-cell secretory capacity [GDM vs. NGT; HOMA-B: 112.63 (83.52 - 143.93) vs. 128.60 (108.77 - 157.58), median (IQR); p = 0.04] and low insulin sensitivity [GDM vs. NGT; HOMA-%S: 43.29 (31.77 - 57.98) vs. 70.42 (56.86 - 86.59), median (IQR); p < 0.001] as shown in Table 2.

Using the cut-off for HOMA-IR at the level of 2.89, it was observed that statistically significant number of GDM women had higher HOMA-IR values in comparison to pregnant women with NGT (GDM vs. NGT; 26.8% vs. 4.9%, p = 0.007) (Table 3).

4. Discussion

Gestational diabetes mellitus (GDM) is a heterogeneous disorder that complicates a certain percentage of all pregnancies. Women with GDM are normally older and tend to be more obese than pregnant women with normal glucose

Table 1. Basic characteristics of the study subjects [n = 82].

Variables	GDM	NGT	p
Study subjects (n)	41	41	
Age (years, mean ± SD)	28.29 ± 3.79	26.22 ± 5.13	**0.041**
BMI (kg/m^2, mean ± SD)	27.16 ± 4.13	25.27 ± 3.01	**0.020**
Gestational weeks (mean ± SD)	29.83 ± 3.63	28.54 ± 3.95	0.127
SBP (mmHg, mean ± SD)	106.46 ± 11.74	107.02 ± 14.18	0.846
DBP (mmHg, mean ± SD)	69.51 ± 9.00	66.83 ± 9.86	0.202
Previous bad obstetric history			
None	28 (68.3)	28 (68.3)	
Macrosomia	2 (4.9)	1 (2.4)	
Abortion	10 (24.4)	10 (24.4)	0.856
IUD	0	1 (2.4)	
Abortion + IUD	1 (2.4)	1 (2.4)	
Family history of DM	18 (43.9)	12 (29.3)	0.169
Previous history of GDM	3 (7.3)	0	0.241*

Values in the parentheses denote the corresponding percentage. Comparison between GDM and NGT group done by Student's t-test and Chi-square-test/Fishers Exact test*. GDM: gestational diabetes mellitus; NGT: normal glucose tolerance; BMI: body mass index; DM: diabetes mellitus; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 2. Insulin indices in GDM and NGT [n = 82].

Variables	GDM (n = 41)	NGT (n = 41)	p
Fasting insulin (μIU/ml)	10.19 (7.71 - 13.34)	6.88 (5.88 - 8.47)	<0.001
HOMA-IR	2.31 (1.73 - 3.15)	1.42 (1.15 - 1.76)	<0.001
HOMA-B	112.63 (83.52 - 143.93)	128.60 (108.77 - 157.58)	<0.04
HOMA-%S	43.29 (31.77 - 57.98)	70.42 (56.86 - 86.59)	<0.001

Values in the parentheses denote the corresponding median interquartile range (IQR); p-values were calculated using Mann-Whitney U test; GDM: gestational diabetes mellitus; NGT: normal glucose tolerance; HOMA-IR: homeostasis model assessment of insulin resistance; HOMA-B: homeostasis model assessment of β-cell function; HOMA-%S: homeostasis model assessment of insulin sensitivity.

Table 3. Frequencies of subjects under HOMA-IR cut-off at 2.89*.

HOMA-IR value	Groups		Chi-square value	p-value
	GDM (n = 41)	NGT (n = 41)		
<2.89	30 (73.2)	39 (95.1)	7.41	**0.007**
≥2.89	11 (26.8)	2 (4.9)		

Significance values obtained from Chi-square-test; Values in the parentheses denote the corresponding percentage; GDM: gestational diabetes mellitus; NGT: normal glucose tolerance; HOMA-IR: homeostasis model assessment of insulin resistance; *Cut-off of HOMA-IR ≥ 2.89 [14].

tolerance (NGT) [8]. Insulin resistance (IR), β-cell dysfunction and decreased insulin secretory capacity appears to be an important factor for development of GDM [8]. The physiological insulin resistance is compensated by a considerable increase in insulin secretion, and hence most pregnant women are able to retain NGT [8].

This study demonstrated that significant older age and higher BMI in GDM women compared to pregnant women with NGT, these findings were consistent with previous studies [4] [8].

In pregnancy, the maintenance of normal glucose homeostasis is dependent upon the capacity of the pancreatic β-cells to markedly increase the secretion of insulin and thereby compensate for the severe physiologic IR [20]. Under influence of various mediators, β-cells undergo structural and functional changes that includes increased β-cell mass and proliferation, increased insulin synthesis and enhanced glucose-stimulated insulin secretion [21]. GDM arises in women in whom this β-cell compensatory response is insufficient, resulting in the hyperglycaemia by which GDM is diagnosed. Thus, GDM is a result of both pancreatic β-cell insufficiency and increased IR, in which genetic predisposition and other factors might be involved [8]. The above mentioned pathophysiologic basis is quite relevant to the rationale for the present investigation of insulin indices in GDM. In this study, Women with GDM showed decreased insulin sensitivity and secretory capacity as measured by HOMA model.

According to WHO 2013 criterion, the 3-samples OGTT was used to diagnose GDM in this study. This criterion labels women with higher glycemic values as "diabetes in pregnancy", who were not encompassed in the study as there might be pre-existing glucose intolerance in this particular group and hence may not be true GDM. To identify the GDM women, subjects underwent OGTT after 24 weeks of gestation were included in this study. Because physiological changes that occur in pregnancy is characterized by progressive IR that begins near mid pregnancy and progresses through the third trimester [17].

Of the many pathogenic mechanisms, IR and impaired β-cell function remain the hallmarks of GDM [20]. This study assessed insulin resistance with fasting insulin and HOMA-IR values, and found those values to be significantly higher in GDM group than in NGT. Insulin secretory index HOMA-B was significantly lower in GDM women than NGT women even with lesser insulin sensitivity as measured by HOMA-%S. Earlier studies also suggested that the pathogenesis of GDM is a defect of islet β-cell functions and compensatory increase in insulin secretion in response to increased IR during pregnancy [22]. Present findings are in line with other reports, that GDM is caused by both reduced insulin secretion and enhanced IR [22] [23] [24] [25].

It is to be noted that fasting serum insulin levels reported in current study were also in agreement with the findings of previous studies [4] [20] [26] [27]. Having high fasting insulin level is known to be an important sign of IR [27].

This study assessed fasting insulin and HOMA-IR values and found those

values to be significantly higher in GDM group than in NGT. At present, there is no universal cut off value to differentiate IR in GDM. In a previous study, HOMA-IR values ≥ 2.89 at diagnosis of GDM were found to have strong correlation with early initiation of insulin therapy and daily insulin requirement [14]. They also suggest that degree of IR, as assessed by HOMA-IR index at the diagnosis of GDM, could be a potential predictor of GDM severity and the future development of type 2 diabetes. In this study, total 11 (26.8%) GDM women were found to have HOMA-IR values ≥ 2.89 ($p < 0.007$). Though it was beyond the scope of this study, it can be advocated that further studies are required to determine the relationship of HOMA-IR with optimal treatment strategies and perinatal outcome.

The present study has certain limitations. First, apart from HOMA model, other indices (like insulin secretion-sensitivity index-2, Matsuda index, insulinogenic index etc.) for estimation of insulin resistance and β-cell dysfunction could not be calculated. Second, we were unable to analyze postpartum glucose tolerance status and other perinatal outcomes of the study subjects.

In summary, GDM women were significantly older and had significantly higher BMI than pregnant women with NGT. HOMA-IR and HOMA-B analysis revealed decreased insulin sensitivity and poorer β-cell function in GDM. Therefore GDM was found to be associated with both insulin resistance and inadequate insulin secretion. Further studies are warranted to elucidate the factors that aggravate insulin resistance and β-cell dysfunction in GDM.

5. Conclusion

This study demonstrated that significantly older age and higher BMI in GDM women compared to pregnant women with NGT. GDM is associated with both insulin resistance and inadequate insulin secretion.

Acknowledgements

The authors greatly acknowledge Department of Biochemistry and Molecular Biology, BSMMU, Dhaka, Bangladesh for their technical support.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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