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Fasting C-peptide in gestational diabetes mellitus

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Abstract

Background: Pregnancy is a state of insulin resistance. Fasting serum C-peptide is used as an indicator of basal insulin secretion, which varies in different trimester in same individual. How the presence of gestational diabetes mellitus (GDM) affects insulin secretion is not well studied in Bangladeshi population.

Objectives: To see the fasting serum C-peptide in subjects with GDM compared to age, body mass index (BMI), and trimester matched control with normal glucose tolerance (NGT) during pregnancy.

Methods: This case-control study investigated fasting serum C-peptide in 72 pregnant women (GDM=37, NGT=35), and compared it between the study groups in different trimester and BMI category. GDM was diagnosed by WHO 2013 criteria. Plasma glucose was measured by the glucose oxidase method and C-peptide by a chemiluminescent immunometric assay.

Results: Among the study participants with BMI ≥25 (n=40) {(GDM=20, NGT=20)}, fasting serum C-peptides was significantly higher in the GDM group than that of the NGT {NGT vs. GDM: 1.25 (0.94-1.82) vs. 1.67 (1.12-2.60); ng/ml, median with IQR, p=0.041} but no difference was observed between GDM and NGT with a BMI <25 kg/m^2 {NGT vs. GDM: 1.19 (0.93-1.53) vs. 1.24 (0.94-1.67); ng/ml, median with IQR, p=0.94}. Within the NGT group, fasting C-peptide was similar with a BMI cut-off 25 kg/m^2 (<25 vs. ≥ 25: 1.19 (0.93-1.53) vs. 1.25 (1.04-1.94); ng/ml, median with IQR, p=0.279, however, within the GDM group, the fasting C-peptide was significantly higher with a BMI ≥25 kg/m^2 {<25 vs. ≥ 25: 1.24 (0.94-1.67) vs. 2.35 (1.38-2.9); ng/ml, median with IQR, p=0.005}. We did not observe any trimester-specific difference of fasting C-peptide between the NGT and the GDM (p=0.675, 0.073, and 0.247 for 1st, 2nd and 3rd respectively trimester), within NGT group (p=0.513) and within GDM group (p=0.489). Spearman's correlation revealed positive and significant correlation between fasting C-peptide and BMI (rho=0.338, p=0.0041).

Conclusion: Fasting C-peptide increased significantly in GDM with BMI ≥25 kg/m^2, but not with <25kg/m^2. *[J Assoc Clin Endocrinol Diabetol Bangladesh, January 2025; 4 (1): 09-14]*

Keywords: C-Peptide, Gestational diabetes mellitus, Bangladesh

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Introduction

Hyperglycemia in pregnancy (HIP), affects one in six pregnancies globally and one in four pregnancies in Southeast Asia. More than 80% of hyperglycemia in pregnancy is caused by gestational diabetes mellitus (GDM).[1] Pregnancy is a state of insulin resistance; and it is the most crucial in the development of GDM. Impaired β-cell function, and insulin secretory defects are also responsible for GDM in lean mothers.[2,3] Impaired insulin secretion accounts for as much as 40% of GDM in leaner women in Japan.[4] There are many causes of defective insulin secretion including

maturity-onset diabetes of the young (MODY), single nucleotide polymorphism (SNP), and others genetic causes. MODY gene mutation has been found in a significant proportion of pregnant women with GDM and young-onset diabetes patients.[5,6] Pregnant women with GDM who carried the risk allele (T) in TCF7L2 rs7903146 displayed significantly lower fasting insulin levels than those in non-carriers.[7] In our population, the majority of pregnant women are under the 30-year age group despite that the prevalence of GDM was found high in a hospital-based study.[8] Screening of islets cell autoantibody, fasting serum insulin, serum C-peptide, and genetic screening may help to identity the underlying causes of GDM but doing all these investigations are not feasible in a low-resource setting; furthermore, not all tests are available everywhere. Measuring fasting C-peptide may be a simple and good alternative for initial screening for insulin secretory status. C-peptide is secreted at equimolar concentration with insulin from beta cells of the pancreas. Insulin has a very short half-life compared to C-peptide (3-5 minutes vs. 20–30 minutes), which affords a more stable test window for fluctuating beta cell responses. Half of all insulin secreted by the pancreatic beta cell is metabolized in the liver by first-pass metabolism; whereas C-peptide has negligible hepatic clearance. C-peptide is cleared in the peripheral circulation at a constant rate, whereas insulin is cleared variably, making direct measurement of serum insulin less consistent.[9] Insulin secretion varies in different trimester in non GDM individual as well subjects with GDM. Normal physiological changes of insulin secretion in different trimester of GDM mother and non GDM mother are not well studied in Bangladeshi people.

This study aimed to see fasting serum C-peptide as an indicator of basal or background insulin secretion among GDM mothers and non GDM/NGT control in different trimester and compare it at different trimester and BMI category. Finding of the study would help to see changes of insulin secretory status in different trimester of both GDM and NGT mother, and guide us to assume underlying pathology of GDM in Bangladeshi people. Finding of this study may be an important clue for further research.

Methods

Study subjects and design: This case-control study was conducted in the Department of Endocrinology of a University hospital. Pregnant women with ages ≥18 to 40 years, gestational weeks of 6 to 38, were recruited from the antenatal clinic, Department of Gynecology & Obstetrics, of the University, from March 2016 to February 2017 after approval by the Institutional Review Board (IRB). Blood samples for pregnancy specific three samples (fasting, 1 hour and 2 hours after oral glucose load) oral glucose tolerance test (OGTT) and fasting serum C-peptide were collected at the GDM clinic of the Endocrinology Department of BSMMU. Blood was centrifuged immediately after collection and transported to the biochemistry and immunology laboratory within 30 minutes of collection for measurement of plasma glucose and serum C-peptide. A total of 35 GDM mothers, and 37 age, BMI, and trimester-matched pregnant women with NGT were included in this study. Pregnancy-specific WHO 2013 criteria were used to define them as either GDM or NGT. Demographic and clinical variables, including height, weight, body mass index (BMI, kg/m^2), and blood pressure (mmHg), were recorded in a structured data collection sheet for analysis. Height was measured by using a stadiometer while standing upright on a flat surface without shoes. Weight was measured with a balance on a hard, flat surface. Blood pressure (BP) was measured in millimeters of mercury by a standard sphygmomanometer.

Analytic method: C-peptide was measured by a chemiluminescent immunometric assay (Siemens 2008, C-peptide, IMMULITE 2000). The reference range of serum fasting C-peptide was 0.9–7.1 ng/ml. Serum glucose was measured by the glucose oxidase method in an automated analyzer [RA-50 analyzer (Dade Behring, Germany)]. Inter-assay co-efficient of variation (CV) for fasting C-peptide was 4.44% and plasma glucose was 5.36% (for low level) and 5.59% (for high level).

Statistical analysis: Distribution of quantitative variables were checked by Shapiro-Wilk test. Quantitative data were expressed in mean± standard deviation (SD) or median with interquartile range (IQR) as applicable, whereas qualitative data were expressed as frequency and percentage. Statistical analyses were performed using IBM SPSS Statistics for Windows version 25.0 (IBM Corp., Armonk, NY, USA). The association between categorical variables was analyzed by the chi-square (χ^2) test and the continuous variable by the Mann-Whitney test. The correlation was done by Spearman's correlation test. For all statistical tests, a p-value of less than 0.05 was considered statistically significant.

Results

The majority of our study population (60%) in both groups were multigravida, and most of them were housewives. The baseline characteristics of the study subjects were similar between the NGT and GDM groups (Table-I).

We observed fasting C-peptides was significantly higher in the GDM group compared to NGT group (p=0.041). We did not observe any significant difference of background insulin secretion between the groups with BMI <25 kg/m^2 (p=0.94), however; the difference was only maintained with BMI ≥25 kg/m^2 (Table-II). Within the NGT group, fasting C-peptide was also similar when compared to the

Table-I: Characteristics of study subjects based on glycemic profile (n=72)

Characters/variables	**Control NGT (n=37)**	**Case GDM (n=35)**	**p**
Age (median, IQR, yr)	26.0 (23-27.5)	26.0 (23-30)	0.544
BMI (mean ± SD, kg/m^2)	25.56±3.60	26.18±4.55	0.524
BMI <25 kg/m^2	17 (45.9%)	15 (42.9%)	0.817
BMI ≥25 kg/m^2	20 (54.1%)	20 (57.1%)	
Systolic BP (median, IQR, mmHg)	110 (100-120)	110 (100-120)	0.216
Diastolic BP (median, IQR, mmHg)	70 (60-80)	70 (60-80)	0.435
Family history of DM	10 (27.0%)	14 (40.0%)	0.319
History of abortion	12 (32.4%)	11 (31.4%)	1.0
Gravida			
Primigravida	15 (40.5%)	14 (40%)	1.0
Multigravida	22 (59.5%)	21 (60%)	
Trimester			
1st Trimester	5 (13.5%)	5 (14.3%)	0.969
2nd Trimester	14 (37.8%)	14 (40.0%)	
3rd Trimester	18 (48.7%)	16 (45.7%)	
Occupation			
Housewife	30 (81.1%)	24 (68.6%)	0.471
Service holder	5 (13.5%)	8 (23.0%)	
Students	2 (5.4%)	3 (8.4%)	

Within parenthesis percentages are expressed over column total.
BMI: Body mass index, expressed in kg/m^2 BP: Blood pressure
Age, Systolic BP and diastolic BP were not normally distributed, so expressed in median with interquartile range (IQR) and analyzed by Mann-Whitney U test
Body mass index (BMI) was normally distributed and analysed by independent sample t test.
Categorical data were analysed by Chi-square test.
GDM: Gestational diabetes mellitus (WHO 2013 Criteria used to define GDM)
NGT: Normal glucose tolerance

Table-II: Comparison of fasting C-peptide between the study groups at BMI cut-off of 25 kg/m^2 (n= 72)

Groups	**Fasting C-Peptide (ng/ml)**		**p**
	NGT (median, IQR)	**GDM (median, IQR)**	
All Subjects (n=72)	1.25 (0.94-1.82) (n=37)	1.67 (1.12-2.60) (n=35)	0.041
BMI <25 kg/m^2 (n=32)	1.19 (0.93-1.53) (n=17)	1.24 (0.94-1.67) (n=15)	0.94
BMI ≥25 kg/m^2 (n=40)	1.25 (1.04-1.94) (n=20)	2.35 (1.38-2.9) (n=20)	0.025
**P value	0.279	0.005	

Whitney test for comparison between NGT and GDM
NGT= Normal glucose tolerance GDM: Gestational diabetes mellitus
BMI= Body mass index

Table-III: Comparison of fasting C peptide between NGT vs. GDM at different trimesters (n=72)

Trimester	Fasting C Peptide (ng/ml)		P value
	NGT (mean ± SD)	GDM (mean ± SD)	
1st Trimester (n=10)	1.40 (1.16-2.02) (n=5)	1.67 (1.10-2.23) (n=5)	0.675
2nd Trimester (n=28)	1.20 (0.94-1.67) (n=14)	2.25 (1.22-3.00) (n=14)	0.073
3rd Trimester (n=34)	1.23 (0.93-1.83) (n=18)	1.39 (1.02-2.42) (n=16)	0.247
P value	0.513	0.489	

NGT= Normal glucose tolerance GDM: Gestational diabetes mellitus
Mann-Whitney test was used to compare fasting C-peptide level of NGT and GDM at different trimester and Kruskal-Walis test was performed to see trimester specific difference of fasting C-peptide within the group

Table-IV: Spearman's correlation of fasting C-peptide with various factors of study subjects (n=72)

Determinants	Correlation coefficient (rho)	P value
Age	0.020	0.908
BMI	0.338	0.041
SBP	0.291	0.08
DBP	0.219	0.193
Week of gestation	-0.147	0.385
FPG	0.151	0.373
1h PG	0.09	0.597
2h PG	0.061	0.720

BMI= Body mass Index in kg/m^2 SBP: Systolic blood pressure
DPB: Diastolic blood pressure FPG: Fasting plasma glucose
1h PG: Plasma glucose at 01 hour of OGTT
2h PG: Plasma glucose at 02 hour of OGTT

BMI cut-off of 25 kg/m^2 (p=0.279). However, within the GDM group, fasting C-peptide was significantly higher in the GDM group with BMI ≥25 kg/m^2 (p=0.005). We did not observe any trimester-specific difference in fasting C-peptide between the NGT and GDM groups (Table-III). Spearman correlation revealed BMI had a significant positive correlation with fasting C-peptide (Table-IV).

Discussion

The fasting C-peptide represent the background insulin secretion. In our study, we observed that fasting C-peptide was significantly higher in the GDM group than that in the NGT group. However, this difference was not observed when we compared C-peptide between GDM and NGT with a BMI <25 kg/m^2. Fasting C-peptide did not significantly differ in the NGT group based on BMI category (<25 vs. ≥ 25 kg/m^2), however; in the GDM group, fasting C-peptide increased significantly with increasing BMI (≥25 kg/m^2). These findings indicate that insulin secretion is increased in GDM with an increasing BMI. However, the subjects who were diagnosed with GDM with a relatively lower BMI had no significantly increased insulin secretion compared to the BMI-matched NGT, despite having higher plasma glucose. This group of GDM mothers might have insulin secretory defects that lead to the development of GDM.

Fakhrul-Alam M. et al. reported the same findings. They assessed the insulin sensitivity and secretory capacity of the GDM mother with age and a BMI-matched control.[3] They observed that insulin secretion was statistically significantly low in GDM mothers compared to NGT mothers with a BMI cut point of <23 kg/m^2. Tania et al. also observed that the fasting C-peptide in GDM mothers was also statistically significantly lower in lean GDM mothers compared to NGT.[10] In our study, it was not low; rather, it was statistically similar between GDM and NGT. This may be due to using a BMI cut-off of 25 kg/m^2 in our study, whereas it was 23 kg/m^2 in the previous study. In our study, we did not observe any significant difference in fasting C-peptide in the NGT group based on BMI category (≥25 vs. <25 kg/m^2). However, ElżbietaPoniedziałek-Czajkowska et al. observed significantly higher concentrations of C-peptide (2.77 ± 1.88 vs. 2.25 ± 1.42 ng/mL, p = 0.034) in the obese NGT group than that of the normal BMI NGT group. This may be due to the very high mean BMI in the obese NGT group compared to the normal BMI group (32.68 ± 5.12 vs. 21.07 ± 2.13, mean±SD, kg/m^2), which was not very high in our study.[11] In another study from China, fasting C-peptide was similar between the GDM and NGT groups during the last trimester of pregnancy and after delivery. We also observed no trimester-specific difference in fasting C-peptide between the GDM and NGT mothers. However, the overall fasting C-peptide in the GDM group was significantly higher than that

of the NGT. There are many causes of insulin secretory defects. Maturity-onset diabetes in the young (MODY) gene mutation is one of the important regions of defective insulin secretion. In one study, screening of GCK, HNF1A, HNF4A, INS, and HNF1B gene mutations in 354 GDM women revealed a significant number of GDM results from these gene mutations. They reported a 5.9% prevalence of possible diabetes-predisposing gene variants. Overall, 11% of the total number of diabetic women at follow-up had diabetes-predisposing variants in GCK, HNF1A, HNF4A, HNF1B, or INS.[13] In another study, the prevalence of MODY gene mutation was 12.6% among South Asian individuals who were referred for MODY testing.[14] A genetic polymorphism of TCF7L2 is also an important cause of defective insulin secretion. The frequency of polymorphism of TCF7L2 was observed to be higher in lean and young-onset GDM mothers studied in Bangladeshi GDM women. The CT/TT genotype was associated with a higher frequency of GDM in women aged <25 years (CT/TT vs. CC: 58.3% vs. 17.4%, p = 0.022) and BMI <25 kg/m^2 (CT/TT vs. CC: 61.5% vs. 18.2%, p=0.024).[15] Our study assessed only fasting C-peptide in GDM as an indicator of background insulin secretion. Low or normal background insulin secretion in GMD mother with BMI <25 kg/m^2 was the main findings in our study which serves as a guide to investigate the genetic basis of GDM with relatively normal body weight and rethink the pathogenesis of GDM in this group.

Our study was done in a tertiary care hospital, which does not represent the population of whole country. Samples of our study was not that much high to reach the final conclusion regarding insulin secretion status in apparently normal weight GDM mother. Large scale study with higher number of samples from multiple centers may be needed to establish our findings and further research. There is no pregnancy specific BMI cut-off to define obesity and overweight. We used an arbitrary BMI of 25 kg/m^2 to compare groups, the findings of the study may be different with BMI cut-off 23 which was done in many other studies. Despite having these limitations, our study provides some basic information regarding background insulin secretion in different trimester both in NGT and GDM groups, which may serve as the foundation for further research in this field.

Conclusions

Insulin resistance was considered the main pathological basis of development of GDM, however; it may be different in relatively normal weight GDM mother. The study findings suggest, low or normal insulin secretion in apparently normal weight GDM mother, which is opposite to the traditional belief. We need large scale study including genetic study to find out pathological basis of GDM in apparently normal BMI GDM mother.

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 upon reasonable request.

Ethical Approval and Consent to Participate

This study was approved by the Institutional Review Board (IRB) of BSMMU, Reg: No. BSMMU/2016/2746, approved on 08-03-2016. All procedures performed in this study involving human participants were following the ethical standards of the IRB and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed written consent was obtained from each of the participants included in the study.

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