

# Homeostatic Insulin Sensitivity Indices Is the Detection of Gestational Diabetes Mellitus

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**Abstract:** Background: Early identification of GDM is strongly warranted for prevention of both maternal and fetal complications, but well known disadvantages of the present methods based on oral glucose challenge reduces the compliance and applicability of these methods in the screening of the disorder. Aims: The study aimed to assess FBG-based insulin sensitivity indices (ISIs) regarding their suitability as alternatives of 2 hr 75-g OGTT. Methods and Materials: Out of 300 subjects, 112 had GDM. Finally 84 GDM and 82 normal mothers were analyzed. A nested case control study was conducted with group of pregnant mothers, at 24 to 32 weeks of gestation, were recruited from BIRDEM (the tertiary hospital of Diabetic Association of Bangladesh) was screened for GDM by adapting WHO criteria. Serum glucose and insulin was measured by glucose oxidase and chemoluminescence based ELISA. (ISIs) as well as glycemic and insulinemic indices were calculated their ability to detect GDM. Homeostatic formulas were used to quantify insulin sensitivity and B-cell function. McNamara test was used to calculate sensitivity, specificity, PPV and NPV of various tests against the gold standard of OGTT. Results: HOMA%B was significantly ( $p<0.001$ ) lower in GDM ( $113.3\pm51.4$ ) than their non-GDM counterparts ( $207.9\pm91.3$ ). In Pearson's correlation, HOMA%B had a significant correlation with age, FBG, 75-g OGTT and fasting insulin level. HOMA%S showed significantly correlation with FBG, 75-g OGTT, fasting insulin, HOMA%B and QUICKI. Logistic regression provided significant association of HOMA%B with GDM ( $p=0.002$ ) after adjusting the effect of the confounders. The value of different screening markers for predicting GDM was explored. HOMA%S at optimum cut-off value of 50 showed sensitivity of 50% and specificity of 56%, with PPV and NPV 56% and 55% respectively. QUICKI had 28% and 31% respectively at an optimum cut-off value of 0.54. Fasting insulin showed 54% and 49% respectively at cut-off value of  $12.9\mu\text{U/ml}$  with PPV 50% and NPV 50%. At an optimum cut-off value of  $5\text{mmol/l}$ , the sensitivity, specificity, PPV and NPV of FBG was 82%, 78%, 79% and 81% respectively. The corresponding value for combined fasting glucose and fasting insulin were 84%, 79%, 82% and 82%. Conclusion: The data suggest that (ISIs), such as simple fasting blood glucose with a cut-off value of  $5.0\text{mmol/l}$ , for Bangladeshi population, seems to be an acceptable test in the detection of GDM.

**Keywords:** GDM, Insulin Indices, Insulin Secretory Capacity, Insulin Sensitivity

## 1. Introduction

Gestational diabetes mellitus (GDM), a state of varying degree of glucose intolerance with onset or first recognition during pregnancy, is important for its obstetrics repercussion. It causes increased risk of maternal and perinatal morbidity and mortality. GDM is the most common medical

complication and metabolic disorder of pregnancy [1]. Prevalence of GDM is increasing worldwide with higher prevalence in South-Asian women. It complicates up to 14% of pregnancy depending upon population described and the criteria used for diagnosis. The well known complications of GDM not only increase the maternal and perinatal morbidity and mortality, also have long term deleterious effect on mothers and their children increasing economic burden of a

country. So early identification of GDM is strongly warranted. But the quest for a definitive screening test for GDM still goes on. In search of a suitable screening test for GDM, several FBG- based insulin sensitivity indices have been tried and showed reasonable accuracy over OGTT in a pilot study abroad. But for the feasibility of performing mass screening it should undergo further evaluation in different populations. So the current study has been carried out to assess several insulin sensitivity indices in search of a definitive screening test for GDM which would be reliable, simple and patient friendly for Bangladeshi population.

## 2. Methodology

On receipt of the consent form, fasting and 2-hour after 75-g glucose, blood sample were collected from volunteers who met under the selection criteria of the study subjects. Detailed socio-demographic data, family history and medical history were recorded on a pre- designed data collection sheet appropriately. All interviews were conducted in the hospital. Physical examination was done and anthropometric measurements (height, weight) of each subject were taken and recorded in a pre designed data collection sheet. Obstetric examination was performed and recorded for every patient. The data and the specimen (blood) were collected in every morning at BIRDEM hospital.

Serum glucose was measured by glucose oxidase method and insulin was assayed with a chemoluminescence based ELISA. Insulin sensitivity indices as well as glycemic and insulinemic indices were calculated and tested for their ability to detect GDM. Homeostatic formulas were used to quantify insulin sensitivity and B-cell function. Data were analyzed by appropriate statistical tests (using SPSS

Windows 11.0). McNamara test was used to calculate sensitivity, specificity, PPV and NPV.

## 3. Results

The GDM group had higher age as compared to control (years,  $M \pm SD$ ,  $28.9 \pm 3.8$ , vs.  $26.7 \pm 4.6$ ,  $p < 0.001$ ). (Table1) HOMA%B was significantly ( $p < 0.001$ ) lower in GDM ( $113.3 \pm 51.4$ ) than their non-GDM counterparts ( $207.9 \pm 91.3$ ). (table2)QUICKI of GDM was  $0.52 \pm 0.03$  and that of control was  $0.55 \pm 0.05$ ; the difference was statistically significant ( $p < 0.001$ ). (Figure1)HOMA%S showed no significant difference ( $p = 0.158$ ) between GDM and non-GDM groups. (Table2)In Pearson's correlation analysis HOMA%B had a significant correlation with age, FBG, 75-g OGTT and fasting insulin level. HOMA%S showed statistically significant correlation with FBG, 75-g OGTT, fasting insulin, HOMA%B and QUICKI. Logistic regression analysis provided significant association of HOMA%B with GDM ( $p = 0.002$ ) after adjusting the effect of the confounders. (Table3)The value of different screening markers for predicting GDM was explored. HOMA%S at optimum cut-off value of 50 showed sensitivity of 50% and specificity of 56%, with PPV and NPV 56% and 55% respectively. (Table4)QUICKI had sensitivity and specificity of 28% and 31% respectively at an optimum cut-off value of 0.54. Fasting insulin showed sensitivity and specificity of 54% and 49% respectively at cut-off value of  $12.9 \mu\text{U/ml}$  with PPV 50% and NPV 50%. At an optimum cut-off value of  $5 \text{ mmol/l}$ , the sensitivity, specificity, PPV and NPV of FBG was 82%, 78%, 79% and 81% respectively. The corresponding value for combined fasting glucose and fasting insulin were 84%, 79%, 82% and 82%.

**Table 1.** Clinical characteristics of the study subjects.

| Variable                | Control (n=82)    | GDM (n=84)       | P Value   |
|-------------------------|-------------------|------------------|-----------|
| Age (yrs)               | $26.7 \pm 4.6$    | $28.9 \pm 3.8$   | $< 0.001$ |
| Gestational week        | $26 \pm 8.9$      | $24.9 \pm 8.3$   | 0.448     |
| Parity                  | 2 (1-7)           | 1 (1-5)          | 0.883     |
| BMI ( $\text{Kg/m}^2$ ) | $26.1 \pm 4$      | $27.2 \pm 4$     | 0.056     |
| SBP (mm of Hg)          | $110.8 \pm 10.84$ | $113.9 \pm 12.6$ | 0.634     |
| DBP (mm of Hg)          | $74.3 \pm 7.9$    | $74.9 \pm 8.7$   | 0.770     |

GDM=Gestational diabetes mellitus; BMI=Body Mass Index; SBP=Systolic blood pressure; DBP=Diastolic blood pressure.

**Table 2.** Glycemic and Insulinemic status of the study subjects.

| Variable                       | Control (n=82)   | GDM (n=84)       | P Value   |
|--------------------------------|------------------|------------------|-----------|
| Fasting blood glucose (mmol/l) | $4.5 \pm 0.73$   | $6.37 \pm 1.6$   | $< 0.001$ |
| 75 gm OGTT                     | $6.62 \pm 6.7$   | $11.0 \pm 3$     | $< 0.001$ |
| Fasting insulin (microU/ml)    | $15.96 \pm 9$    | $13.6 \pm 3.2$   | 0.039     |
| Fasting insulin (picomole/l)   | $110.8 \pm 63.1$ | $94.4 \pm 22.1$  | $< 0.001$ |
| HOMA%B                         | $207.9 \pm 91.3$ | $113.3 \pm 51.4$ | $< 0.001$ |
| HOMA%S                         | $50.9 \pm 15.9$  | $48.6 \pm 10.1$  | 0.158     |
| GIR                            | $0.34 \pm 0.11$  | $0.49 \pm 0.1$   | $< 0.001$ |
| QUICKI                         | $0.55 \pm 0.05$  | $0.52 \pm 0.03$  | $< 0.001$ |

GDM=Gestational diabetes mellitus; OGTT=Oral Glucose Tolerance; HOMA%B=Homeostasis Model Assessment of  $\beta$  cell capacity; HOMA%S = Homeostasis Model Assessment of Insulin Sensitivity; GIR=Glucose Insulin Ratio; QUICKI = Quantitative Insulin Sensitivity Check Index

**Table 3.** Correlation of HOMA%B and HOMA%S with other variables of the study subjects.

| Variable                       | HOMA%B all subjects (n=166) |        | HOMA%S all subjects (n=166) |        |
|--------------------------------|-----------------------------|--------|-----------------------------|--------|
|                                | r                           | p      | r                           | p      |
| Age (yrs)                      | -0.168                      | 0.030  | -0.078                      | 0.319  |
| Fasting blood glucose (mmol/l) | -0.688                      | <0.001 | -0.212                      | 0.006  |
| 75 gm OGTT                     | -0.524                      | <0.001 | -0.155                      | 0.044  |
| Fasting insulin (microU/ml)    | 0.682                       | <0.001 | -0.836                      | <0.001 |
| HOMA%B                         | -                           | -      | -0.369                      | <0.001 |
| HOMA%S                         | -0.369                      | <0.001 | -                           | -      |
| QUICKI                         | -0.017                      | 0.827  | 0.905                       | <0.001 |
| GIR                            | -0.821                      | <0.001 | 0.452                       | <0.001 |

HOMA%B=Homeostasis Model Assessment of  $\beta$  cell capacity; HOMA%S = Homeostasis Model Assessment of Insulin Sensitivity; GIR=Glucose Insulin Ratio; QUICKI = Quantitative Insulin Sensitivity check Index

**Table 4.** Predictive values of different marker in the study subjects (n=166).

| Variable                            | Percentile       | Cut-off Value | Sensitivity (%) | Specificity (%) | PPV(%) | NPV(%) |
|-------------------------------------|------------------|---------------|-----------------|-----------------|--------|--------|
| Fasting Glucose and Fasting Insulin | 25 <sup>th</sup> |               | 1%              | 2%              | 61%    | 1%     |
|                                     | 50 <sup>th</sup> |               | 84%             | 79%             | 82%    | 82%    |
|                                     | 75 <sup>th</sup> |               | 27%             | 1%              | 1%     | 66%    |
| HOMA%B                              | 25 <sup>th</sup> | 104.7         | 54%             | 1%              | 36%    | 2%     |
|                                     | 50 <sup>th</sup> | 138.9         | 22%             | 23%             | 23%    | 22%    |
|                                     | 75 <sup>th</sup> | 203           | 71%             | 56%             | 14%    | 36%    |
|                                     | 15 <sup>th</sup> | 37            | 13%             | 82%             | 44%    | 48%    |
|                                     | 20 <sup>th</sup> | 39.4          | 21%             | 81%             | 54%    | 50%    |
| HOMA%S                              | 25 <sup>th</sup> | 42            | 29%             | 79%             | 59%    | 52%    |
|                                     | 30 <sup>th</sup> | 44            | 36%             | 76%             | 62%    | 54%    |
|                                     | 50 <sup>th</sup> | 50            | 55%             | 56%             | 56%    | 55%    |
|                                     | 25 <sup>th</sup> | 0.50          | 73%             | 10%             | 45%    | 29%    |
| QUICKI                              | 50 <sup>th</sup> | 0.54          | 28%             | 31%             | 3%     | 30%    |
|                                     | 75 <sup>th</sup> | 0.57          | 10%             | 58%             | 20%    | 39%    |

PPV=Positive predictive value; NPV= Negative predictive Value, HOMA%S=Homeostasis Model Assessment of Insulin Sensitivity; GIR=Glucose Insulin Ratio; QUICKI=Quantative Insulin Sensitivity check Index

## 4. Discussion

Today the majority of women with GDM have features of type 2 diabetes, and are older, more obese and of higher parity [2]. In the present study we analyzed age, parity and BMI by a case-control comparison. Only age of the patient was found to be different between GDM and non-GDM groups. On average GDM mothers were 2.26 years older than controls ( $p<.001$ ).

The HOMA-S is closely correlated with ISI assessed by the euglycemic clamp method which is regarded as the 'gold standard' for insulin resistance[3]. However, euglycemic clamp is complex, requires multiple blood sampling and is inconvenience in pregnancy[4]. A criticism of the HOMA-S is its deviation from linearity with increasing insulin resistance; consequently, it is believed to be an inaccurate index for those with advanced type 2 diabetes[5]. Thus, the author claimed that HOMA-S provided a weaker predictive index compared to QUICKI which is based on a logarithmic and reciprocal transformation of a single fasting glucose and insulin value [5]. The model is very similar to HOMA and differs only in the treatment of the data. This has been validated against the isoglycemic-hyperinsulinemic clamp and was found to have a good linear correlation ( $r^2 = 0.61$ )[4]. Measuring insulin sensitivity by a fasting method

(like HOMA%S or QUICKI) is not only simpler but also noninvasive requiring only a single venipuncture. It is cheaper, less labor-intensive and less time consuming [6]. In our study, for measuring insulin resistance among GDM and non-GDM, HOMA-S and QUICKI were compared by using sensitivity and specificity calculations based on insulin resistance with ROC analysis. Among these ISIs HOMA%S shows more sensitivity and specificity followed by QUICKI. The 50th percentile of cut-off value (54) was found to be optimum where the sensitivity of HOMA%S was 55% and PPV 56% (Table 4). For QUICKI the maximum sensitivity and PPV were found at 25th percentile cut-off value (45% and 29% respectively) (Table 4). These findings are reflected in a study by [6] on comparing HOMA, GIR and QUICKI to measure insulin sensitivity. But Katz et al [5] contradicted us by suggesting QUICKI as a novel, accurate and reproducible method for determining insulin sensitivity. Kirwan et al [4] also demonstrated HOMA as a weaker predictive index compared with QUICKI. Though area under curve (AUCs) that were derived from the ROC curves for HOMA%S and QUICKI were statistically significant, the sensitivity and predictivity of HOMA%S and QUICKI are not high (Table 4). Since the failure to detect 44% of cases of GDM by HOMA%S and 55% of cases by QUICKI, they leave a large number false negative case and may not be considered as

reliable tests in the detection of GDM. Our observation is not reflected by finding of Kauffman [7] who revealed comparable sensitivity and specificity of HOMA (68% and 74.5%) and QUICKI (87.5% and 57%) with others common screening tests.

A study by Buchanan *et al* [8] suggested that  $\beta$ - cell dysfunction is a common, if not universal, feature of GDM. The HOMA% B is the calculation based on fasting glucose and insulin concentrations to percent B-cell function using a mathematical model. This test has been well correlated with insulin-mediated glucose disposal assessed by the glucose clamp technique[3]. In our study, the GDM cases exhibit the significant defect in secretory capacity of beta cell (Table 2). From ROC curve analysis HOMA%B shows more sensitivity and specificity than ISIs (Table4). In fact there is evidence in favor of a predominant role of beta cell dysfunction in the genesis of type 2 diabetes in Bangladeshi population[9].Xiang *et al* [10] also found that GDM had a 67% reduction in their beta cell compensation compared with normal pregnant control subjects. Kauffman *et al* [7] argued against the use of HOMA%B independently as screening tools. Because it is impossible to ascertain whether increased level of insulin is in response to mounting insulin resistance or decreased level due to B-cell dysfunction. However HOMA%B has been claimed to be more suitable for large epidemiological studies [3].

When none of the ISIs, HOMA%B or fasting insulin was found to show a reasonably high level of sensitivity, specificity, PPV or NPV, an analysis was made with FBG as a marker. The AUC (0.883) derived from the ROC curve for FBG was highly significant and it was found to be the best predictor of GDM. The best cut-off value from the ROC curve was found to be 5.0mmol/l and with this cut-off point the sensitivity and specificity of this simple parameter were 82% and 78% respectively, and the PPV and NPV were 79% and 81% (Table 4). This finding strongly corresponds with observation by Kauffman [7]. They demonstrated FBG as the single most discriminatory test at cut-off value of 92mg/dl (5.01 mmol/l) (sensitivity 76% & specificity 89.8%) for the diagnosis of GDM. In another study, Perucchini [11] also showed FBG (using a cut-off value of 4.8mmol/l with sensitivity of 81% specificity of 76%) as an easier means of screening for GDM than glucose based test. There is disagreement with Kausta *et al* [12] who found that a single fasting glucose screen failed to identify 60% of women with abnormal 2 hour blood glucose levels. There are several other studies [13,11,14-16] concluded that FBG demonstrates equal or better sensitivity and specificity to screen for GDM than 50g OGTT which is recently recommended as universal screening [7,17,18]. Metzger *et al* [19] showed that a 1-hour 50g OGTT would have 80% sensitivity at cut-off value of 140mg/dl and the sensitivity can be increased to 90% further decreasing the threshold to 130mg/dl. This cut-off value will increase the number of women who require a 3-hour 100g OGTT 25% and consequently will increase the cost of identifying each case of GDM. Again some authors [11,20] found that 50g OGTT had relatively poor sensitivity.

Kauffman *et al* [7] supported that feasibility of FBG as a screen with great consideration, though women with postprandial hyperglycemia and fasting normoglycemia would be missed. The screening value of FBG can only be marginally improved by combining it with fasting insulin (sensitivity 84%, specificity 79%, PPV 82% and NPV 82%) (Table 4). Combining the substantial cost of insulin assay this improvement in PPV and NPV may not be justified as a routine procedure.

## 5. Conclusion

The study results suggest that the insulin sensitivity indices do not seem to be reliable alternatives for the detection of GDM. Rather simple fasting blood glucose (with a cut-off value of 5.0mmol/L for Bangladeshi population.

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