Risk of Future Diabetes is as High with Abnormal Intermediate Post-Glucose Response as with Impaired Glucose Tolerance

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Abstract

Aims: This analysis was done to compare the risk of development of diabetes among subjects with impaired glucose tolerance (IGT) and early glucose intolerance (EGI; intermediary post glucose level $\geq 160$mg/dl) when compared with normal (NGT). Profile of insulin secretion and insulin resistance was compared in a subgroup of subjects with EGI, IGT and diabetes.

Patients and Methods: A program on ‘primary prevention of diabetes’ was initiated and high risk subjects were encouraged to join the program and were followed up. Out of 4084 (M: F 2344 : 1740) subjects enrolled in the program, a total of 1659 (M:F 1044 : 615) subjects with mean age 41.3 ± 10.2 years who had atleast two follow up visits were selected for this analysis. OGTTs were performed once in every 6 months. The median follow up duration was 5 years. The conversion rate to diabetes in subjects with persistent IGT or EGI was determined. In a subgroup of subjects, NGT (n = 118), IGT (n = 68), EGI (n = 106) and new DM (n = 126), plasma insulin at fasting, 30 min and 2 hr were measured and insulin resistance (HOMA - IR) was calculated by HOMA method. Insulinogenic index ($\Delta I/ G$) was also calculated.

Results: The rate of conversion of IGT 251 (40.5%) and EGI 210(36.5%) subjects to diabetes was similar and significantly higher when compared with the NGT subjects 99 (21.3%). Similar results were noted both in men and women. By using ROC procedure, a cut – off value of one hour post glucose of $\geq 160$ mg/dl gave a sensitivity of 80% and specificity of 70% to detect abnormal glucose tolerance. In a subset of subjects studied, it was noted that subjects with EGI had significantly higher fasting insulin values than NGT. Insulin resistance (IR) was the highest in DM [Geometric mean (SD)] 6.6(1.9), followed by EGI (4.5(2.3)) (p < 0.0001 vs NGT, 2.9(2.4)) and IGT (3.9(2.2)). Insulinogenic index was normal in EGI, NGT and IGT, and it was lower in DM in comparison with other groups. The multiple logistic regression analysis showed that EGI (odds ratio (OR) 2.11) and development of diabetes was strongly associated. The survival curve (time free from diabetes) showed that the median survival time for NGT, EGI and IGT were 18.7, 11.6 and 9.6 yrs respectively.

Conclusion: EGI which is a distinct entity with abnormal intermediate glucose response in glucose tolerance test (GTT) appears to be a risk factor similar to IGT in the development of diabetes. They had higher insulin resistance with normal insulin secretion. Therefore, it is important to determine the intermediate value also during the GTT in addition to fasting and 2 hr post glucose values.

INTRODUCTION

According to the latest WHO criteria, the cut off for the normal fasting plasma glucose (FPG) is $< 110$ mg/dl ($< 6.1$mmol/L) and for 2-hour post glucose (2-hr PG) is $< 140$ mg/dl ($< 7.8$ mmol/L). The diagnostic cut-off point for diabetes (DM) of $\geq 200$ mg/dl ($\geq 11.1$ mmol/L) for the 2-hr PG has been justified largely because approximately at that point, the prevalence of microvascular complications specific for diabetes (i.e. retinopathy and nephropathy) increases dramatically. The FPG cut-off for diagnosis of DM of 126 mg/dl (7mmol/L) is based on the belief that the cut points for FPG and 2 – hr PG should diagnose similar conditions and associations with vascular complications. The relationship of FPG and 2-hr PG to the development of retinopathy were evaluated in PIMA Indians over a wide range of plasma glucose cut points. Both variables were similarly associated with retinopathy indicating that by this criteria, each could work equally well for diagnosing diabetes. The studies were confirmed by similar studies in...
The terms IGT (impaired glucose tolerance) and IFG (impaired fasting glucose) refer to a metabolic state intermediate between normal glucose homeostasis and diabetes, now referred to as pre–diabetes. IFG and IGT are not clinical entities in their own right but rather risk factors for future diabetes and cardiovascular diseases.1

In the diagnostic criteria for glucose intolerance, no mention is made about the plasma glucose responses intermediate to the fasting and 2hr during an OGTT. Many non-diabetic subjects show isolated abnormal intermediate values above 160 mg/dl (8.9 mmol/L) with fasting plasma glucose < 110 mg/dl (< 6.1 mmol/L) and the 2 hr value < 140 mg/dl (< 7.8 mmol/L). In an earlier study, we had reported that larger percentage of subjects having an early glucose intolerance (EGI; i.e. elevated intermediate post glucose value) deteriorated to diabetes than normoglycaemic subjects.2 This prospective study was done to compare the risk of developing diabetes among subjects with IGT and EGI compared with normal (NGT) subjects. The profile of insulin secretion and insulin resistance in a subgroup of subjects with NGT, IGT, EGI and diabetes was also studied.

**Patients AND METHODS**

A program on “primary prevention of diabetes” was initiated in view of the high prevalence of diabetes in the population and high risk subjects i.e. those with positive family history of diabetes were encouraged to join the program. A total of 4084 (M: F 2344 : 1740) subjects were enrolled and were followed up in this program. Out of 4084 subjects 1659 (M: F 1044 : 615) subjects with mean age of 41.3 ± 10.2 years and who had at least two follow up visits were selected for this analysis. A standard oral glucose tolerance test (OGTT) with 75 gms anhydrous glucose load was done and diagnosis was made according to the WHO criteria.1 Normal glucose tolerance (NGT) was diagnosed if the fasting and 2hr values were <110 mg/dl (< 6.1 mmol/L) and < 140mg/dl (< 7.8 mmol/L). Impaired glucose tolerance (IGT) was diagnosed if the 2hr value is 140 – 199 mg/dl (7.8 – < 11.1 mmol/L). Early glucose intolerance (EGI) was diagnosed if one hour value is ≥ 160mg/dl (≥ 8.9 mmol/L) during OGTT. All the subjects underwent second OGTT to confirm the diagnosis and were included in the study.

Subjects with known history of diabetes, newly diagnosed diabetes during the screening were excluded. Age, height and weight measurements were recorded and body mass index (BMI kg/m²) was calculated. Subjects were given advice on preventive measures such as dietary modifications and regular exercise. They were followed up and a reminder letter to undergo OGTT was sent to all the subjects once in every 6 months. The median follow up duration was 5 years. Among the 1659 subjects, a subgroup of 418 subjects, 118 non-diabetic subjects, 68 subjects with IGT, 106 subjects with EGI and 126 subjects with diabetes were taken for subanalysis. The ethics committee of the institution approved the study. Written informed consent was obtained from all the study participants.

A receiver operating curve (ROC) curve showed that ≥ 160 mg/dl (≥ 8.9mmol/L) had 80% sensitivity and 70% specificity to detect abnormal glucose tolerance.

Venous blood samples were collected to estimate the biochemical parameters. Plasma glucose was estimated by glucose oxidase peroxidase method7 at fasting and at half an hour intervals for 2 hour after glucose load. Insulin was estimated in plasma samples on fasting, 30 minutes and 2 hour post glucose samples. Insulin assay was done using the RIA kit supplied by Diasorin (Italy). The sensitivity of insulin assay was less than 4 µU/ml. The intra and interassay CVs were less than 10.6 and 10.8% respectively.

Insulin resistance (HOMA – IR) and insulinogenic index (Δ I/ G) were calculated in the subgroup of subjects.

Insulin resistance was determined using the HOMA calculation8 which was

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\text{Insulin resistance (HOMA - IR) = fasting insulin (µU/ ml) } \times \text{ fasting glucose (mmol /L) } / \text{22.5}
\]

Insulinogenic index (Δ I/ G) = 30 min insulin – fasting insulin (pmol/L) / 30 min glucose (mmol/l)

**Statistical Analysis**

Statistical analysis was performed using SPSS version 10.0 (SPSS, USA). Data with normal distribution were expressed as mean ± S.D. A receiver operating curve (ROC) was used to determine the optimal cut-off point in the one hour post glucose value to diagnose EGI. Insulin values were corrected for BMI and fasting insulin, 2 hr insulin, HOMA – IR and Δ I/ G were log transformed and expressed as geometric mean and S.D. One-way ANOVA was used to determine the differences across the groups. Comparison of proportions was done by chi-square test. A multiple logistic regression analysis was used to determine the factors associated with development of diabetes. Cox’s regression analysis was done to see the factors influencing the conversion to diabetes. A survival curve was plotted using life table method to determine the survival time for the NGT, IGT and the EGI subjects. Wilcoxon (Gehan) test was done for comparing the survival distribution between the groups. Bonferroni correction method was used to adjust the p values for multiple comparisons. A p value of < 0.05 was considered significant.

**RESULTS**

A total of 1659 (M:F 1044 : 615) subjects who had undergone OGTTs periodically and had at least two followup visits were included in this analysis. The median follow up duration was 5 years. In the total subjects 33.8% had developed diabetes. Table 1 shows the baseline anthropometric and biochemical characteristics of the study groups. The mean age and body mass index of EGI and IGT subjects were significantly higher than NGT subjects. Table 2 shows the conversion rate of NGT, EGI and IGT subjects to diabetes in the total group and men and women separately. There was a significant difference between the conversion
rate among NGTs 99 (21.3%) and EGI 210 (36.5%) in the total group (χ² = 27.8; p<0.0001). Similar rates were seen both in men (χ² = 18.0; p<0.0001) and women (χ² = 9.0; p=0.003).

The percentage of subjects who developed diabetes during follow up was significantly lower in NGT 99 (21.3%) compared to IGT 251 (40.5%) (χ² = 44.2; p<0.0001). But there was no significant difference in the conversion rate between the EGI (36.5%) and IGT (40.5%) (χ² = 1.9; p = 0.15). Similar results were observed both in men (χ² = 2.3; p=0.12) and women (χ² = 0.03; p=0.9) also.

The risk of diabetes was similar in IGT and EGI versus NGT subjects and no difference (p>0.05) was noted in age (42 ± 9.7 yrs vs 42.4 ± 9.8 yrs), positive family history (21% vs 18%) and BMI (27.4 ± 4.1 kg/m² vs 27.1 ± 4.1 kg/m²). It was interesting to note that EGI subjects had the highest BMI when compared with the other groups. By the ROC analysis, a cut–off value of one hour post glucose of ≥ 160 mg/dl gave a sensitivity of 80% and specificity of 70% to detect abnormal glucose tolerance.

The characteristic features of the subgroup showed that the IGT, EGI and diabetic subjects were older than the non-diabetic subjects (p<0.05). However, no difference in age was noted between IGT, EGI and diabetic subjects (Table 3).

EGI had significantly higher fasting insulin values than NGT. The 2-hour insulin values were found to be the highest in the IGT followed by the EGI and diabetic subjects. HOMA-IR was the highest in DM (Geometric mean 6.6 SD (1.9)), followed by EGI (4.5(2.3)) (p < 0.0001 vs NGT, 2.9(2.4)) and IGT (3.9 (2.2)). Early phase insulin secretion denoted by insulinogenic index (ΔI/G) was normal in EGI, NGT and IGT (NGT - (ΔI/G) is 61(2.0), Geometric mean (SD)) EGI. 59 (2.1), IGT 58(1.8). (ΔI/G) in DM (15 (2.4)) was significantly lower in comparison with other groups (Table 3).

Table 4 shows the results of multiple logistic regression analysis. It showed that EGI (odds ratio (OR) 2.11) had a

<table>
<thead>
<tr>
<th>Baseline</th>
<th>NGT</th>
<th>EGI</th>
<th>IGT</th>
</tr>
</thead>
<tbody>
<tr>
<td>N, total (men:women)</td>
<td>NGT 465 (265:200)</td>
<td>EGI 575 (388:187)</td>
<td>IGT 619 (391:228)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>38.7 ± 10.9</td>
<td>42.0 ± 9.7*</td>
<td>42.4 ± 9.8*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.2 ± 4.6</td>
<td>28.7 ± 4.8</td>
<td>28.1 ± 4.6</td>
</tr>
<tr>
<td>Plasma glucose (mg/dl)</td>
<td>Fasting 96.9 ± 10.4</td>
<td>105.3 ± 11.4*</td>
<td>109.6 ± 12.2**</td>
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<td>175.9 ± 25.9*</td>
<td>173.6 ± 24.1*</td>
</tr>
<tr>
<td>2 hr. after oral glucose load</td>
<td>109.6 ± 17.4</td>
<td>118.3 ± 17.7*</td>
<td>160.1 ± 17.2**</td>
</tr>
</tbody>
</table>

*p < 0.05 Vs NGT; **p < 0.05 Vs EGI by ANOVA.

Table 2 : Conversion rate to diabetes among NGT, EGI and IGT subjects

<table>
<thead>
<tr>
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*p < 0.05 Vs NGT; **p < 0.05 Vs EGI by ANOVA.

Table 3 : Characteristics of the sub-study groups

<table>
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<tr>
<th>Characteristics of the sub-study groups</th>
<th>Normal Glucose Tolerance (NGT) (n = 118)</th>
<th>Impaired Glucose Tolerance (IGT) (n = 68)</th>
<th>Diabetes (n = 126)</th>
<th>Early Glucose Intolerance (EGI) (n =106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>40 ± 11</td>
<td>46 ± 11*</td>
<td>44 ± 9*</td>
<td>44 ± 11*</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24 ± 4</td>
<td>25 ± 4</td>
<td>25 ± 3</td>
<td>27 ± 4*</td>
</tr>
<tr>
<td>Fasting insulin (µU/ml)</td>
<td>12.4 (2.2)</td>
<td>15.7 (2.5)</td>
<td>15.4 (2.6)</td>
<td>17.9 (2)*</td>
</tr>
<tr>
<td>2- hr insulin (µU /ml)</td>
<td>53 (2.5)</td>
<td>118 (2.2)</td>
<td>59 (2.5)#</td>
<td>101 (2.5)</td>
</tr>
<tr>
<td>Insulin resistance (HOMA – IR)</td>
<td>2.9 (2.4)</td>
<td>3.9 (2.2)</td>
<td>6.6 (1.9)*</td>
<td>4.5 (2.3)</td>
</tr>
<tr>
<td>Insulinogenic Index (ΔI/G)</td>
<td>61 (2.0)</td>
<td>58 (1.8)</td>
<td>15 (2.4)*</td>
<td>59 (2.1)</td>
</tr>
</tbody>
</table>

*p vs NGT  # vs IGT  $ vs Diabetes  (p value < 0.01)
significant association with development of diabetes. The higher OR was for EGI followed by IGT (OR 1.89), Family history of diabetes (OR 1.82), BMI (OR 1.02), fasting plasma glucose (OR 1.0) and 2hr post glucose (OR 1.01) (Table 4).

Cox's regression analysis confirmed the above result and showed that EGI ($\beta = 0.66, OR = 1.94, p < 0.001$) had influence on the development of diabetes. The other parameters associated with conversion to diabetes were initial BMI ($\beta = 0.038, OR = 1.04, p < 0.001$), IGT ($\beta = 0.45, OR = 1.57, p < 0.009$), FPG ($\beta = 0.008, OR = 1.01, p = 0.02$) and 2hr PG ($\beta = 0.009, OR = 1.01, p < 0.001$).

The survival curve showed that the median survival time for NGT was 18.7 years for EGI it was 11.6 yrs and for IGT it was 9.6 yrs. The comparison of survival experience showed that there was a significant difference in the median survival time across the groups.

**DISCUSSION**

The risk conferred by postprandial hyperglycaemia is being increasingly recognised. These changes are apparent much earlier than in fasting glucose regulation and has significant clinical implications. It is a well-established fact that in the natural history of type 2 diabetes, most individuals pass through a phase of IGT. Stages of IGT and IFG have abnormal insulin action and the comorbid associations of insulin resistance with cardiovascular risk factors are shown to have serious implications. Epidemiological data show that both these conditions significantly increase the risk of CVD and diabetes. Abnormal post-prandial handling of a glucose challenge can be due to inadequate action of insulin on target tissues. This study has shown that EGI, an intermediary post glucose abnormality had risks similar to IGT in the development of diabetes. The importance of IFG and IGT has validated the use of fasting and 2 – hour post glucose testing. However when only these two tests are performed, subjects with EGI are missed out.

EGI was noted to be associated with insulin resistance rather than a $\beta$ - cell defect. EGI subjects had higher insulin resistance when compared with normal subjects. As the $\beta$ cells are minimally affected, it may be possible to revert the glucose intolerance by measures to reduce insulin resistance. Lifestyle modifications including dietary modifications and enhanced physical activity are likely to be beneficial in EGI subjects also, as they have been found to be beneficial in reducing insulin resistance. These interventions are beneficial in prevention of conversion of IGT to diabetes.

EGI subjects in this study had higher BMI compared with the other study groups. EGI was found to confer higher risk for development of diabetes (OR 2.11) when compared with IGT or other risk factors. To further strengthen the argument that EGI was a risk factor for diabetes, the survival curve showed that the duration free from diabetes was lesser in EGI subjects than the NGT subjects. As EGI is commonly encountered in the Asian Indian subjects, and as it is associated with the pathophysiology predisposing to diabetes, it is an entity that needs to be recognised as a prediabetic condition.

Although the OGTT is an acceptable diagnostic test and has been an invaluable tool in research, it is not recommended for routine screening purpose. Because of its inconvenience to patients and the perception by many physicians that it is unnecessary, the OGTT is used only for diagnosing diabetes. This study showed that doing merely the fasting and 2hr post glucose may not be sufficient and it may be necessary to determine the intermediate value also during an OGTT to detect this abnormal intermediate glucose response. In summary, this study suggests that an abnormal intermediate post glucose response also should be looked upon in the diabetic screening in subjects with a high risk for the disease, in order to identify this prediabetic condition. There is not much data regarding this prediabetic condition and more studies need to be done in other populations also. Studies on EGI in different populations will show the significance of this abnormal profile of glucose tolerance.

**REFERENCES**

1. Definition, Diagnosis and classification of diabetes mellitus and its


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**Announcement**

**XIV th National CME in Haematology and Haemato-Oncology, Bombay Hospital, Mumbai. 3-6 January 2008 (Thur-Sun)**

For all the details including registration form: Prof. M.B. Agarwal, MD, Haematology Centre, Ghamat Lodge, 804-A, Dr. B Ambedkar Road, Dadar TT, Mumbai - 400 014.

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