Insulinogenic indices among type 2 Diabetic Nigerians

Adamu G Bakari
Department of Medicine, Ahmadu Bello University Teaching Hospital, Zaria, Nigeria

Abstract
Abnormal pancreatic beta cell function is known to occur in type 2 diabetes mellitus. However, direct measurement of pancreatic beta cell function is cumbersome and virtually out of reach of most laboratories in developing countries. Fortunately, insulinogenic indices may be used as surrogate measures of beta cell function. To study insulinogenic indices among type 2 diabetic Nigerians. A cross sectional study involving 40 type 2 diabetic patients and 36 age- and sex-matched control subjects was undertaken. Diabetic patients and control subjects underwent standard oral glucose tolerance tests (OGTT). Fasting and post OGTT plasma insulin levels were measured using an ELISA technique, while plasma glucose levels were determined by a glucose oxidase method. Insulinogenic indices were calculated at time 30, 60, 90 and 120 minutes of OGTT. Diabetic subjects and controls were statistically compared. At 30, 60 and 90 minutes of OGTT, type-2 diabetic patients had significantly much lower insulinogenic indices compared to control subjects (p < 0.001). At 120 minutes of OGTT, however, the difference between the two groups was not statistically significant. Only BMI showed a positive correlation with insulinogenic index at 30 minutes of OGTT (r = +0.607, p < 0.001). There was no significant correlation between insulinogenic indices and duration since diagnosis of diabetes mellitus. Type 2 diabetic patients exhibit lower insulinogenic indices suggesting poor pancreatic beta cell function. (Int J Diabetes Metab 13: 167-169, 2005)

Key words: Insulinogenic index, pancreatic beta-cell function, type 2 diabetes, Nigerians, OGTT

Introduction
Pancreatic beta cell function is abnormal in type 2 diabetes mellitus. However, direct measurement of pancreatic beta cell function is cumbersome considering the sophisticated equipment needed to carry out "euglycaemic clamp studies", a method considered as the "gold" standard in measuring beta cell function and insulin sensitivity. In most developing countries however, non availability of equipment makes clamp studies virtually impossible. There is therefore the need to use surrogate measures of pancreatic beta cell function which could be obtained using relatively simple methodology.

The term "insulinogenic index" introduced in 1967 by Setzler et al. refer to a ratio obtained by dividing increments of plasma insulin levels above fasting values by the relative net increase of plasma glucose levels; reflects dynamic interactions between plasma insulin and glucose levels. The index could therefore provide an insight regarding the pancreatic beta cell response to changing levels of plasma glucose.

Racial factors seem to be important modulators of insulinogenic indices. To date there are no reported studies on the insulinogenic indices among type 2 diabetic Nigerians.

This information is vital for a better understanding of this heterogeneous and multifactorial metabolic disorder.

Subjects and Methods
Type 2 diabetic patients attending the diabetic clinic of Ahmadu Bello University Teaching Hospital (ABUTH) Zaria and had “good” glycaemic control, defined as fasting blood sugar (FBS) of 4.4 to 6.7 mmol/L; and or a 2 hour post prandial (PP) blood sugar of 4.5 to 8.9 mmol/L and 'acceptable' glycaemic control (FBS of 6.8 to 7.8 mmol/L and or 2h PP of 9.0 to 10.0 Mmol/L) on at least three clinic visits while on dietary therapy alone, or dietary therapy in addition to oral hypoglycaemic agent(s) formed the subjects of this study. Classification of patients as type 2 diabetic was, however, based on clinical grounds of non dependence on insulin for survival. The exclusion criteria were insulin dependence, evidence of secondary diabetes, current insulin therapy or previous history of ketoacidosis.

Thirty-six healthy volunteers who were similar in age, sex and socio-economic status (using educational levels and income) with no personal or family history of diabetes mellitus or hypertension acted as controls. The exclusion criteria also include clinical evidence of any illness and current use of any form of medication.

Information on age, sex and anthropometric measures were obtained from all patients and control subjects. Weights (in Kg) were taken with only undergarments to the nearest 0.5kg. Heights (in metres) were taken to the nearest 0.5cm with subjects standing erect without shoes or headgear.
Body Mass Index (BMI) was derived by dividing the weight by the square of the height.\(^7\)

**Metabolic Studies**

All patients were instructed to stop oral hypoglycaemic agent therapy a week before metabolic studies to eliminate the effect of these drugs on insulin secretion.\(^3\) Following an overnight 10-12 hours fast commencing between 21.00 to 22.00 hours the preceding night, 5mL of venous blood were drawn from each subject into EDTA-treated tubes and promptly centrifuged. Plasma glucose analysis was done within an hour of collection using a glucose oxidase method. Aprotinin 200 KIU per ml of plasma\(^4\) was added to the aliquot set aside for insulin assay and kept at -20\(^\circ\) C until analyzed.

Plasma insulin assays were performed using a commercially available ELISA human insulin kit (DRG instruments GmbH, Marburg, Germany, Cat no. EIA 2935). The kit has an inter-assay and intra-assay coefficients of variation of 5.2 \(\pm\) 4.8\%, respectively. The sensitivity of the kit for human insulin was 99\% and has no cross-reaction with pro-insulin. Plasma glucose analysis was done within an hour of collection of the plasma using a glucose oxidase method\(^5\).

Insulinogenic indices were calculated by dividing increments of plasma insulin above fasting values by the corresponding increment of plasma glucose levels above the fasting plasma glucose values\(^4,5\).

Results are presented as mean \(\pm\) standard deviation. Two-tailed unpaired student's t-test was used to determine the differences between continuous variables, while chi-square test was used for categorical variables. Pearson's correlation coefficient was used to define correlation between variables. The level of statistical significance in each case was taken as \(P < 0.05\).

**Results**

A total of 40 (28 males and 12 females) type 2 diabetic patients and 36 (24 males and 12 females) control subjects participated in the study. Average age at time of study was 49.4 \(\pm\) 9.7 years (range 36 to 70 years) for type 2 diabetic patients and 48.6 \(\pm\) 9.8 years (range 36 to 69 years) for control subject (\(P>0.5\)). Male: female ratio was 2.3:1 for type 2 diabetic patients and 2:1 for control subjects (\(P > 0.5\)).

Type 2 diabetic patients had significantly higher body mass indices (BMI) than control subjects. Mean BMI was 24.93 \(\pm\) 4.43 Kg/M\(^2\) for diabetic patients and 22.93 \(\pm\) 4.02 Kg/ M\(^2\) for controls, (\(p <0.05\)). Furthermore, eight (22.2\%) of the control subjects had BMI of \(\geq 25\)Kg/M\(^2\) compared to 16 (40\%) of the type-2 diabetic patients.

Average duration of diagnosis of diabetes was 5.6 \(\pm\) 4.3 years (range 1 to 20 years). Diabetes mellitus was diagnosed in 26 (65\%) of the subjects less than 5 years before the study. Fifteen (37.5\%), of the diabetic patients had 'good' glycaemic control, while 25 (62.5\%) had 'acceptable' glycaemic control at entry into the study. All the diabetic patients required oral hypoglycaemic agents in addition to dietary measures for glycaemic control (25 on Chlorpropamide alone, 12 on Chlorpropamide and metformin and three on metformin alone).

There were marked variations in individual insulinogenic indices among type 2 diabetic patients and control subjects. This variation notwithstanding, type 2 diabetic patients had significantly lower indices at 30, 60 and 90 minutes of OGTT, at 120 minutes of OGTT however, the difference was not significant (table 1). There was no significant difference between the insulinogenic indices of diabetic patients who had "good" glycaemic control and those who had "acceptable" glycaemic control at entry into the study (\(p > 0.1\) at 30, 60, 90 and 120 minutes).

There was no significant correlation between insulinogenic indices among type 2 diabetic patients and BMI, age and duration of diabetes (Table 2).

**Discussion**

Insulinogenic indices represent dynamic interactions between changing levels of plasma insulin and changing levels of plasma glucose. In this study, control subjects expectedly had significantly and consistently higher indices than their type 2 diabetic counterparts. This could be explained by the fact that in control subjects, as blood glucose levels increased, there was a proportional and adequate insulin response. In the type 2 diabetic patients however, despite higher increments of post OGTT plasma glucose, only modest changes of plasma insulin occurred leading to a much lower ratio, consistent with a state of impaired pancreatic beta-cell function.\(^4\) This finding is expected and similar to earlier findings in Indian and African South-African type 2 diabetic patients.\(^5\) At 120 minutes of OGTT however, insulinogenic indices among type 2 diabetic patients and the controls were similar. This could be explained by the adequate beta-cell response in the control group with resultant prompt clearance of ingested glucose resulting in less stimulation of the beta cell thereafter.

Studies suggest an early pancreatic beta-cell failure as the operative defect in black type-2 diabetic patients, which led Joffe and Seftel \(^10\) to postulate a decrease in the mass of functioning beta cells as a key factor in the aetioapathogenesis of type-2 diabetes in Black South-Africans. In this study however, it is impossible to suggest whether the low insulinogenic indices is the cause of, or as a result of type-2 diabetes mellitus, since it is known that hyperglycaemia causes as well as aggravates pancreatic beta cell failure.\(^11\)

There was no significant correlation between the duration of diabetes and insulinogenic indices (a surrogate of beta cell function). A previous study in South Africa by Omar and Asma\(^6\) could not demonstrate any relationship between plasma insulin levels (and by extension beta cell function) and duration of diagnosis of diabetes. Difficulties with establishing the actual period of onset of type 2 diabetes may contribute to a large margin of error and probably mask the influence of the duration of diabetes if there is any.
Table 1: Insulinogenic indices among type 2 Nigerian diabetic patients and control subjects

<table>
<thead>
<tr>
<th>OGTT time</th>
<th>Insulinogenic indices mean ± SD</th>
<th>Table 1: Correlation between insulinogenic indices and other variables among type 2 diabetic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type 2 diabetics (n=40)</td>
<td>Control Subjects (n=36)</td>
</tr>
<tr>
<td>30 minutes</td>
<td>0.56 ± 0.38</td>
<td>4.56 ± 2.83</td>
</tr>
<tr>
<td>60 minutes</td>
<td>0.40 ± 0.23</td>
<td>4.31 ± 2.34</td>
</tr>
<tr>
<td>90 minutes</td>
<td>0.57 ± 0.28</td>
<td>3.19 ± 1.92</td>
</tr>
<tr>
<td>120 minutes</td>
<td>0.99 ± 0.56</td>
<td>1.61 ± 1.05</td>
</tr>
</tbody>
</table>

Table 2: Correlation between insulinogenic indices and other variables among type 2 diabetic patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Insulinogenic Index At 30 minutes</th>
<th>Insulinogenic Index At 120 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>r = + 0.6070, p &lt; 0.001</td>
<td>r = - 0.2228, p &gt; 0.05</td>
</tr>
<tr>
<td>AGE</td>
<td>r = - 0.2151, p &gt; 0.05</td>
<td>r = - 0.1423, p &gt; 0.1</td>
</tr>
<tr>
<td>Duration of diabetes*</td>
<td>r = + 0.0026, p &gt; 0.5</td>
<td>r = - 0.0200, p &gt; 0.5</td>
</tr>
</tbody>
</table>

* Refers to the duration since diagnosis of diabetes.

Although individuals with "good" glycaemic control are expected to exhibit better insulinogenic indices than those with "acceptable" glycaemic control, as the effect of glucose toxicity is expected to be less marked with better glycaemic control. This study did not show a significant difference between the two groups. This could be due to the use of blood sugar only to categorize patients in this study. The categorization might have been better if tests that are less likely to be affected by short-term changes in blood sugar such as glycosylated haemoglobin or fructosamine were employed.

The strong correlation between insulinogenic indices at 30 minutes and BMI among type 2 diabetic patients suggests that those with higher BMI tend to exhibit better early insulin responses. It is, however, difficult to suggest the relevance of this finding. However, it is possible that individuals with the insidious form of type 1 diabetes whose clinical features are identical to that of type 2 diabetes, but typified by the presence of anti-glutamic acid decarboxylase (anti-GAD) antibodies were included as only clinical criteria were used to classify patients as type 2-diabetic.

It is concluded that type-2 diabetic patients in this study exhibit lower insulinogenic indices compared to control subjects, suggesting poor pancreatic beta cell response to changing levels of plasma glucose.

References