Total insulin output is low in type-2 diabetic Nigerians

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Abstract

Background: Plasma insulin levels among type 2 diabetic patients are modulated by racial and ethnic factors. In contrast to the plethora of reported studies on plasma insulin levels among type 2 diabetic patients in technically advanced regions of the world, there is paucity of such information in Africa in general. **Objective:** To study insulin output among type 2 diabetic Nigerians. **Subjects and methods:** Forty type-2 diabetic and 36 healthy subjects underwent a standard oral glucose tolerance test (OGTT). Fasting and post OGTT plasma insulin levels were measured using an ELISA technique. Integrated insulin responses were calculated using trapezoidal estimation to compute total insulin output. Student's t test was used to compare means; the level of statistical significance in each case was taken as $p \leq 0.05$. **Results:** The age and sex distribution of diabetic patients and control subjects were similar ($p > 0.5$). Average duration of diabetes was 5.6 ± 4.3 years (range 1 -20 years) Total insulin output was significantly lower among type 2 diabetic patients than in control subjects (360 ± 82.1 micro-units per ml and 745.1 ± 109.0 micro-units per ml respectively $P<0.00$ 1). **Conclusion:** Type-2 diabetic patients in this study exhibit hypoinsulinaemia; this could be the explanation for the pattern of diabetic complications among type 2 diabetic Nigerians observed in previous studies.

Key words: insulin, type-2 diabetes, Nigerians, hypoinsulinaemia

Introduction

Both hypoinsulinaemia and hyperinsulinaemia have been reported among type 2 diabetic patients[1,2] and more importantly, some of the chronic complications of diabetes mellitus are related to prevailing plasma insulin levels.[3] Racial factors seem to play modulatory roles in these diverse responses. In South Africa for example, type 2 diabetic Africans exhibit lower plasma insulin levels compared to their Indian counterparts[4]. The few studies on plasma insulin levels in Nigeria concentrated on healthy volunteers and relatives of type 2 diabetic patients.[5, 6] There is as yet no reported study of the plasma insulin pattern in Nigerian type 2 diabetic patients as opposed to the vast literature on the subject in technically more developed countries. We studied the total insulin output in response to a standard OGTT among type 2 diabetic patients.

Patients and methods

All patients and control subjects studied were drawn from a single ethnic group (Hausa-Fulani) around the city of Zaria (located at Longitude 08° 30° East and latitude 04° 00° North) in Northern Nigeria. Type 2 diabetic patients attending the diabetic clinic of Ahmadu Bello University Teaching Hospital (ABUTI-1) Zaria and having 'good' glycaemic control, defined as fasting blood sugar (FBS) of 4.4 to 6.7 mmol/L, and or a 2 hour post prandial blood sugar of 4.4 to 8.9 mmol/L and 'acceptable' glycaemic control (FBS of 6.7 to 7.8 mmol/L and or 2 HPP of 8.9 to 10.0 mmol/L)[7] on at least three clinic visits while on dietary

therapy alone, or dietary therapy in addition to oral anti-diabetic 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.[8] The exclusion criteria were insulin dependence, evidence of secondary diabetes, current insulin therapy, previous history of ketosis, pregnancy or use of oral contraceptives, and clinical or biochemical evidence of disease of the liver, kidney or thyroid.

Thirty-six healthy volunteers who had no personal or family history of diabetes mellitus or hypertension were recruited to serve as controls. The exclusion criteria were clinical evidence of any illness, personal or family history of diabetes mellitus or hypertension, and current use of any form of medication.

Information on age, sex and anthropometric measurements were obtained from all patients and control subjects. Weights (in Kilograms) were taken with the patients wearing only undergarments to the nearest 0.5 kg. Heights (in metres) were taken to the nearest 0.5 cm with subjects standing erect without shoes or headgear. Body Mass Index (BMI) was derived by dividing the weight by the square of the height.[9]

Metabolic studies

Institutional ethical committee approval was granted before the commencement of the study and informed consent was obtained from all patients and control subjects. Oral hypoglycaemic agent therapy was withdrawn a week before metabolic studies to eliminate the effect of these drugs on insulin secretion.

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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. Glucose analyses were done within an hour of collection of the plasma using a glucose oxidase method.[10] Aprotinin 200 KIU/ ml of plasma was added to the aliquot for insulin assay;[11] this was kept at -20°C until analysis.

Following the withdrawal of the fasting sample, each subject had an intravenous canular left *in situ* with a slow infusion of saline (3-5 drops per minute) to maintain patency. Anhydrous glucose (75 grams dissolved in 300ml of water) was given to each subject, and each of them completed this within 5 minutes. The time of the first sip was recorded as time zero minute of the OGTT. Blood samples were taken at times 30, 60, 90 and 120 minutes of the OGTT and handled the same way as the fasting blood samples. Patients and control subjects were observed in the metabolic laboratory and discharged home only when in satisfactory condition.

Plasma insulin assays were performed using a commercially available ELISA human insulin kit (DRG instruments Gmbh, Marburg, Germany, Cat no. EIA 2935). This kit has a sensitivity of 99% for human insulin, inter-assay and intra-assay coefficients of variation of 5.2% and 4.8% respectively, and no cross-reaction with pro insulin. Total insulin output was derived by trapezoid estimation from time zero minutes to 120 minutes of OGTT.[12]

Results are presented as mean ± standard deviation. Unpaired student's t-test was used to determine the differences between continuous variables and 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 type 2 diabetic patients and 36 control subjects participated in the study. Average age at time of study was 49.4 ± 9.7 years (range 36 to 70 years) for type 2 diabetic patients and 48.6 ± 9.8 years (range 36 to 69 years) for control subject (P>0.5). Similarly, the sex distribution for the two groups was also similar (P > 0.5). Nine (23%) of the control subjects were overweight compared to 16 (40%) of the type 2 diabetic patients (p<0.05). Type 2 diabetic patents had significantly higher body mass indices than control subjects with respective mean and standard deviation values of 24.93 ± 4.43 KgM^{-2} for diabetic patients versus 22.93 ± 4.02 KgM^{-2} for controls (p <0.05).

Average duration of diagnosis of diabetes was 5.6 ± 4.3 years (range 1 to 20 years). Fifteen (37.5%), of the diabetic patient had 'good' glycaemic control, while 25 (62.5%) had 'acceptable' glycaemic control at entry into the study. All the diabetic patients required oral hypoglyceamic 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 the individual total insulin output following oral glucose challenge. Total insulin output was similarly lower among type 2 diabetic patients, 360 ± 82.1 micro-units per ml as against 745.1 ± 109.0 micro-units per ml in the controls (p<0.001). There was no significant correlation between plasma insulin levels and BMI among type 2 diabetic patients (r +0.057, p>0.5).

Discussion

Despite much higher blood glucose levels Type 2 diabetic patients demonstrated lower total insulin output. This could be explained by the failure of pancreatic beta cells to respond appropriately to the prevailing blood glucose levels. The hypoinsulinaemia observed among type 2 diabetic patients in this study, is in agreement with earlier studies in African [4,13,14] and African-American [6] type 2 diabetic populations, but contrary to findings in most European studies.

Hypoinsulinaemia seems to be the rule in African, and African-American type 2 diabetic patients. In South Africa, Omar and Asmal in a study of 14 young (age less than 35 years) African patients with type 2 diabetes and 10 African controls, demonstrated lower plasma insulin levels in the diabetic group in the fasting state as well as following the OGTT[4]. This was similar to the findings of Asmal and Leary in older African type 2 diabetic patients.[13] It is possible that the underlying defect in African type 2 diabetics is predominantly pancreatic beta cell malfunction leading to hypoinsulinaemia. Osei *et al* were able to demonstrate that African-Americans even at near normal and normal blood glucose levels demonstrate some beta-cell dysfunction.[15]

There are suggestions that the prevailing plasma insulin levels modulate some of the chronic complications of diabetes mellitus. Whereas hyperinsulinaemia is known to be associated with macrovascular complications and cardiovascular morbidity and mortality in at least some populations,[1,2,8] Partanen and colleagues demonstrated that hypoinsulinaemia is a significant risk factor for the development and progression of diabetic peripheral neuropathy irrespective of the degree of glycaemic control.[3] This could explain the pattern of complications of diabetes such as high prevalence of peripheral neuropathy and relative rarity of ischaemic heart diseases seen in this environment.[16]

Obesity is known to lead to insulin resistance with resultant hyperinsulinaemia. A positive correlation between plasma insulin levels and the degree of obesity is therefore expected. In this study, however, there was no significant correlation between plasma insulin levels and BMI similar to the findings of Aronoff,[17] who in a comparative study of plasma insulin levels in Caucasians and Pima Indians, noted lack of association between the degree of obesity and fasting plasma insulin levels among Caucasians but a positive association among Pima Indians suggesting a role for racial factor in the relationship between BMI and plasma insulin levels.

We conclude that type 2 diabetic patients in this study demonstrate hypoinsulinaemia and suggest that prospective studies be undertaken to define the spectrum of insulin response in our environment.

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