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Glucose and Insulin responses in offspring of Nigerian Type 2 diabetics

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Summary
Type 2 diabetes mellitus has a strong genetic basis as evidenced by a concordance rate ranging between 60 and 90% in monozygotic twins. Glucose and insulin responses to an oral glucose load were measured in 52 offspring of Nigerian Type 2 diabetics and 50 control subjects selected to achieve a similar distribution of age and gender. All subjects studied were glucose tolerant. In comparison with control subjects, offspring of Type 2 diabetics had a significantly higher mean (SD) (i) fasting plasma glucose level [69.2 (13.0) mg/dl vs. 62.2 (7.6) mg/dl; P=0.0012] (ii) fasting plasma insulin level [26.6 (15.4)μIU/ml vs. 14.8 (6.8)μIU/ml; $P<0.0001$] (iii) 2 hours post glucose load plasma insulin level [59.8 (33.9)μIU/ml vs.40.9 (24.2)μIU/ml; P=0.0028]. The mean (SD) 2-hour post glucose load plasma glucose level did not differ significantly between both groups of subjects [92.8 (23.8) mg/dl vs. 85.5 (21.3) mg/dl; $P=0.11$]. Further multiple regressional analysis showed that the differences in fasting plasma insulin and 2-hour post glucose load insulin observed were only accounted for by the presence of a parental history of diabetes and were not influenced significantly by BMI, waist and hip circumferences. This study shows that offspring of Nigerian Type 2 diabetics have hyperinsulinaemia, despite being glucose tolerant and this supports the insulin-resistance hypothesis for Type 2 DM. This implies that they are at a greater risk for developing diabetes mellitus and are therefore an important group for the primary prevention of Type 2 DM.

Keywords: *Type 2 diabetes mellitus, offspring, glucose and insulin responses.*

Résumé
Le diabete mellitus du type 2 a une base genetique solide comme le montre le taux concordance allant de 60-90% chez les jumeaux monocygotes. La reponse du glucose et de l'insuline a une charge de glucose administer oralement a ete mesuree chez 52 nouveaux nes Nigerians ayant le diabete type 2 et 50 sujets de controle selectionnes pour atteindre une distribution similaire d'age et du genre. Tous les subjects etudies toleraient le glucose. Em comparaison aux sujets de controle, les progenitures diabetiques de type 2 avaient une moyenne significative (SD) elevee. (i) niveau du glucose dans le plasma a jeun (69.2 (13.0) mg.dl vs 62.2 (7.6) mg/dl ; $P = 0.002$) (ii) niveau de l'insuline dans le plasma a jeun (26.6 (15.4) lcv/ml contre 14.8 (6.8) lcv/ml; $P < 0.0001$) (iii) niveau d'insuline chargi dans le plasma après 2 heutres d'ingestion du glucose (59.8 (33.9) icv/ml contre 40.9 (24.2) icv/ml; $P = 0,0028$). La moyenne (SD) de (iii) ne differrait pas significativement entre les deux groups (92.8 (23.8) mg/dl contre 85.5 (21.3) mg/dl; $P = 0.11$) Davantage, l'analyse multiple regressionelle a montre que les differences en (ii) et (iii) etaient prise en consideration senlement par la presence d'une historique parebtale du diabete et n'etuient pas significativement influences par BMI, la tour de hanche et de la taille. Cette etude montre que les progenitures Nigeri ans diabetiques du type 2 ont l'hyperinsulinaemie, bien que tolerant le glucose et ceci supporte l'hypothese de l'insuline resistance du type 2 DM. Ceci implique qu'ils ont un risqué eleve de developer le diabete mellitus et sont ainsi un groupe important de la prevention primaire du type 2 DM.

Introduction

Type 2 diabetes mellitus (DM) accounts for the majority of diabetics seen in Ibadan [1] It is believed to develop as a consequence of the interaction between genetic and environmental factors [2] Type 2 DM has a strong genetic component as shown by a concordance rate ranging between 60- 90% in monozygotic twins [3,4] Type 2 DM has a strong familial tendency and the presence of Type 2 DM in a first degree relative is an established risk factor for Type 2 DM. First degree relatives of diabetics also have an increased risk of developing diabetes, ranging from 25-50% compared to 15% in first degree relatives of non diabetics [5].

Several laboratories have resorted to investigating the primary metabolic abnormalities in Type 2 DM, in young persons with a familial and genetic predisposition to the disease later in life. This approach is based on the premise that persons with an increased risk for the disease would manifest clusters of metabolic or hormonal alterations that are different or more prevalent than in healthy persons without a family history of diabetes, bearing in mind that insulin secretion and action are familial and inheritable traits [6]. These studies have been used to gain insight into the temporal order of defects in Type 2 DM, as well as to identify metabolic abnormalities in first degree relatives of Type 2 diabetics that may precede and predict subsequent progression to Type 2 DM. This has important implications for the primary prevention of Type 2 DM. The aim of this study was to determine glucose and insulin responses to an oral glucose load in offspring of Type 2 diabetic Nigerians as compared with a control group.

Materials and methods

The study was conducted at the University College Hospital (U.C.H) Ibadan, a city located in the South Western part of Nigeria. The study group consisted of 52 apparently healthy offspring of patients with Type 2 DM attending the diabetic clinic of the hospital. Offspring recruited in the study were those between the ages of 20 – 40 years.

A control group of 50 was also selected consisting of offspring of persons with no known history of Type 2 DM as could be ascertained by a detailed interview. The control group selected also had no other first degree relative known to be diabetic to the best of their knowledge. The control group was selected to achieve a similar distribution of age, gender and socio-economic class Ethical clearance was obtained from the Joint University of Ibadan/ University College Hospital ethical committee. Informed consent was obtained from all patients involved in the study.

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Exclusion criteria

1. Any of the study or control group on drugs that might interfere with glucose metabolism e.g., oral contraceptives, corticosteroids, thyroid hormones.
2. Any of the study or control group already known to be diabetic.
3. Any member of the control group with a first degree relative known to be diabetic.

The subjects were asked to report to the medical out patient clinic after an overnight fast of 12 hours. On arrival subjects were seated and after a few minutes rest, a questionnaire was administered to obtain relevant biodata. Information on the physical activity status (based on patient's occupation, extra leisure time physical activity, etc), usual dietary pattern (traditional African diet or mainly westernized) and use of alcohol and cigarettes were all obtained. The weight (kg) of each person was recorded without them wearing a coat, jacket, shoes or agbada, using a beam type scale. Height (metres) was also measured without the subjects wearing shoes, caps or headgear and standing with the back to the measuring rod, and looking straight ahead. The body mass index (B.M.I) was subsequently calculated using the formula weight (kg)/height [2] (metres) [2].

The waist circumference was measured using a flexible tape measure to the nearest 0.5cm at the level of the umbilicus with the subject standing and breathing normally. The hip circumference was measured with the same tape to the nearest 0.5 cm at the level of the greater trochanter [7]. All measurements were made by the author with an assistant to cross check that the tape measure did not slant. The waist to hip ratio was then calculated. Subjects were then seated and allowed to rest for 5 minutes, following which a blood specimen was taken after cleaning the skin with methylated spirit using a new sterile disposable needle and syringe. Venous blood was collected into a fluoride oxalate bottle for estimation of fasting plasma glucose and into an E.D.T.A. bottle for estimation of fasting plasma insulin. Samples were centrifuged soon after to obtain plasma, which was stored at –20 °C until analysis.

Immediately after the fasting samples were taken, subjects were given a glucose preparation consisting of 82.5 gn of dextrose monohydrate (equivalent to 75gn of anhydrous dextrose) dissolved in 300mls of water to be drunk over 5 minutes. The subjects then rested in the clinic till 120 minutes after they had drunk the glucose after which another blood specimen was drawn after cleaning the skin with a new sterile needle and syringe. The blood was collected into a new dry clean fluoride oxalate bottle and an E.D.T.A. bottle for estimation of plasma glucose and plasma insulin, respectively. All blood samples were promptly centrifuged to separate the plasma. This was stored at -20 °C till analysed for fasting glucose and insulin as well as 2 hours post-glucose load blood glucose and insulin concentrations.

Plasma glucose concentrations were determined by using a glucose oxidase method using 4 aminophenazone as oxygen acceptor as described by Trinder [8]. Plasma insulin concentrations were measured by radioimmunoassay (RIA) using ICN pharmaceuticals IMMU- chem. Coated tubes Insulin I^{125} RIA kit Lot no INK 9981, order no 06-D1884. The assays were conducted at the Chemical Pathology laboratory of the University College Hospital Ibadan.

Statistical analysis

Results are expressed as means (SD) except where otherwise stated. Comparisons between means were performed using the student-test for unpaired data. Chi square test of significance was used to compare proportions. An analysis of covariance was performed to identify any confounding variables on the differences observed between study and control subjects. The level of significance was taken to be $P < 0.05$.

Results

Characteristics of offspring of Type 2 diabetics and control subjects

The age and gender distribution of the offspring of diabetics and control subjects are shown in Table 1. The mean (SD) age for the offspring of diabetics was 28.8 (6.7) years, and for the control subjects it was 29.1 (6.1) years. The mean ages of the offspring of diabetic and control subjects were similar ($P = 0.81$). Both groups were also were well matched for gender as shown in Table 1 ($P = 0.84$).

Table 1: Characteristics of offspring of type 2 diabetics and control subjects

Parameters	Offspring of diabetics parents n = 52	Controls subjects n = 50	Level of significance (P)
Mean age*	28.8 (6.7)	29.1 (6.1)	0.81
Gender			
Male	26 (50%)	24 (48%)	0.84
Female	26 (50%)	26 (52%)	
Weight (kg)	69.9 (15.1)	63.8 (11.3)	0.024
BMI (Kg/m2)	25.0 (4.9)	23.0 (3.0)	0.013
Waist circumference (cm)	82.3 (12.2)	77.2 (8.3)	0.014
Hip circumference (cm)	99.0 (11.4)	93.5 (7.2)	0.005
Waist-Hip ratio	0.83 (0.06)	0.82 (0.05)	0.52

Values are expressed as means (SD)
n = number of subjects

The frequency distribution according to tribe, socio-economic class and educational status did not differ significantly between the 2 groups ($P > 0.05$). The physical activity status, alcohol consumption and smoking history of the offspring of diabetics and controls did not differ significantly ($P > 0.05$). Mainly traditional Nigerian diets were consumed by 49 (94.2%) of the offspring of diabetics and 47(94%) of controls.

The offspring of type 2 diabetics had a significantly higher mean (SD) weight, BMI, waist and hip circumference than the control subjects ($P < 0.05$) as shown in Table 1. However, mean waist-hip ratio (WHR) did not differ in both groups of subjects ($P = 0.52$). Table 1 shows the characteristics of offspring of Type 2 diabetics and control subjects.

Biochemical characteristics of offspring of Type 2 diabetics and control subjects

i. *Blood glucose levels in offspring of Type 2 diabetics and control subjects*

All the 52 offspring of diabetic parents and all the control subjects had normal glucose tolerance. The biochemical characteristics of the offspring of diabetic parents are compared with these control subjects in Table 2.

Table 3 shows biochemical characteristics of study subjects according to gender. Offspring of diabetics had significantly higher mean (SD) fasting plasma glucose than the control subjects [69.2 (13.0) mg/dl versus 62.2 (7.6) mg/dl; $P = 0.0012$] as shown in Table 2. The mean (SD) fasting plasma glucose in male offspring of diabetics was 69.3 (12.1) mg/dl and this was significantly higher than the level in the male control subjects of 60.6 (8.2) mg/dl ($P = 0.00047$) as shown in Table 3.

Table 2: Biochemical characteristics of offspring of type 2 diabetics and controls.

Parameters	Offspring of diabetics	Controls	Level of significance (P)
Fasting plasma glucose (mg/dl)	69.2 (13.0) n = 52	62.2 (7.6) n = 50	0.0012
2 hrs post glucose load plasma glucose (mg/dl)	92.8 (23.8) n = 52	85.5 (21.2) n = 50	0.11
Fasting plasma insulin (μIU/dl)	26.2 (15.4) n = 51	14.8 (6.8) n = 45	<0.0001
2hrs post glucose load plasma insulin (μIU/dl)	58.5 (34.8) n = 51	40.9 (24.2) n = 45	0.0028

Values are expressed as means (SD)
n = number of samples assayed

ii *Plasma Insulin levels in offspring of diabetics and control subjects*

There was a significantly higher mean fasting plasma insulin concentration in offspring of diabetics than in controls. The mean (SD) fasting plasma insulin was 26.6 (15.4)μIU/ml in offspring of diabetics and 14.8 (6.8)μIU/ml in the control subjects ($P < 0.0001$). The 2-hour post-glucose load plasma insulin concentration was also significantly higher in the offsprings of diabetic parents than in controls ($P < 0.0001$). These results are presented in Table 2.

When gender comparisons were made amongst offspring of diabetics and control subjects, mean (SD) fasting plasma insulin level in male offspring of diabetics was also significantly higher [28.7 (16.5)μIU/ml] than in control subjects [13.8 (5.6)μIU/ml] ($P = 0.0004$) (Table 3). Among female offspring of diabetics and female controls subjects, mean fasting plasma insulin concentrations were 24.3(14.1)μIU/ml, and 15.7(7.8)μIU/ml respectively, and this difference was statistically significant ($P = 0.004$) (Table 3).

The mean two hours post-glucose load plasma insulin concentrations were significantly higher in offspring of diabetics than in control subjects [59.8 (33.8)μIU/ml versus 40.9 (24.2)μIU/ml; $P = 0.0028$] (Table 2). Gender comparisons revealed a similar picture, with significantly higher means (SD) two hour post glucose load plasma insulin in male offspring of diabetics [53.1 (30.2)μIU/ml] than in male control subjects [36.1 (25.1)μIU/ml] ($P = 0.039$) (Table 3). The mean two-hour post glucose load plasma insulin in female offspring of diabetics was 66.9 (36.6)μIU/ml compared with 45.5 (23.0)μIU/ml in female control subjects ($P = 0.019$) (Table 3).

Table 3: Biochemical characterisitics of male and female offspring of type 2 diabetics and controls

Parameters	Male offspring of diabetics	Controls	Level of significance (P)	Female offspring of diabetics	Controls	Level of significance (P)
Fasting plasma glucose (mg/dl)	69.3 (12.1) n = 26	60.6 (8.2) n = 24	0.0047	69.1 (14.1) n = 26	63.7 (6.8) n = 24	0.079
2 hrs post glucose load plasma glucose (mg/dl)	92.8 (22.0) n = 26	96.6 (22.8) n = 24	0.33	92.7 (25.9) n = 26	84.6 (20.2) n =24	0.21
Fasting plasma insulin (μIU/ml)	28.7 (16.5) n = 26	13.8 (5.6) n = 22	0.0004	24.3 (14.1) n = 25	15.7 (7.8) n = 23	0.0004
2 hrs post glucose load plasma insulin (μIU/ml)	53.1 (30.2) n = 26	36.1 (25.1) n = 22	0.039	66.9 (36.6) n = 25	45.5 (23.0) n = 23	0.019

Values are expressed as means (SD)
n = number of samples assayed

The mean (SD) fasting plasma glucose in female offspring of diabetics was also slightly higher than that of female controls [69.1 (14.1) mg/dl versus 63.7) 6.8) mg/dl] but this was not statistically significant ($P = 0.079$) (Table 3). Mean (SD) two hour plasma glucose load was not significantly different between the offspring of diabetics [92.8 (23.8) mg/dl] and controls [85.5 (12.3) mg/dl] ($P = 0.11$). A similar pattern was seen when two-hour post-glucose load plasma levels were compared in male subjects and female subjects (Table 3).

A multiple regressional analysis showed that differences in fasting plasma insulin and 2 hour post glucose load plasma insulin were only accounted for by the presence of a parental history of diabetes and were not influenced significantly by BMI, waist and hip circumferences. This is shown in Table 4.

No gender specific parental effects were observed when the biochemical characteristics were compared according to parental history of Type 2 DM as shown in Table 5

Table 4: Multiple regressional analysis for effects of BMI, waist and hip circumferences on fasting plasma insulin and 2 hours post glucose load plasma insulin.

	Fasting			2 hours post glucose load		
	Standardized coefficients	t	Level of significance (P)	Standardized coefficients	t	Level of significance (P)
(Constant)		1.733	.087		1.219	.226
Subject	.484	5.058	.000	.280	2.728	.006
BMI	.378	1.574	.119	.328	1.273	.206
Waist*	2.839	1.675	.097	2.139	1.176	.243
Hip*	-2.580	-1.848	.068	-1782	-1.189	.237

**Circumference*

Table 5: Biochemical characteristics of male and female offspring of diabetics with a paternal or maternal history of Type 2 diabetes mellitus.

Parameters	Males Paternal n = 16	Maternal n = 9	Level of significance (P)	Females Paternal n = 11	Maternal n = 14	Level of significance (P)
Fasting plasma glucose (mg/dl)	70.4 (13.2)	66.3 (10.1)	0.56	68.2 (13.0)	69.1 (15.8)	0.88
2hr post glucose load plasma glucose (mg/dl)	95.3 (17.8)	88.0 (29.6)	0.54	90.3 (29.3)	92.2 (23.2)	0.85
Fasting plasma insulin (μIU/ml)	32.9 (18.8)	21.7 (9.5)	0.10	25.3 (5.3)*	24.4 (17.9)	0.87
2hr post glucose load plasma insulin (μIU/ml)	55.8 (29.4)	50.6 (33.7)	0.69	63.0 (27.1)	62.8 (38.2)	0.98

*Values are expressed as mean (SD); n = number of samples assayed; *n=10*
The two study subjects with both parents diabetic were not included on this table

Discussion

This study set out to compare glucose and insulin responses in offspring of Nigerian Type 2 diabetics with controls selected to achieve a similar distribution for age and sex.

The results of the study showed that the offspring of diabetics had significantly higher mean fasting and 2 hours post-glucose load plasma insulin concentrations accompanied by significantly higher mean fasting plasma glucose concentration. The two hours post glucose load plasma glucose concentration did not differ significantly in the two groups of subjects.

Migdalis *et al* [9] have reported higher fasting and post glucose load plasma insulin concentrations in offspring of Type 2 DM patients. Reports of fasting hyperinsulinaemia amongst Caucasian [10,11,12] and Mexican American [13] offspring of diabetics also corroborate the findings in this study.

Ezenwaka *et al.* [14] did not observe fasting hyperinsulinaemia amongst first degree relatives of Nigerian Type 2 diabetics, a finding at variance with the reports earlier discussed. They however observed a rebound hyperinsulinaemia during the latter phase of the insulin secretory response to an intravenous glucose load and evidence suggestive of reduced tissue insulin sensitivity (i.e., insulin resistance).

In assessment of insulin responses to a glucose challenge, it is noted that some studies utilised frequently sampled glucose tolerance tests (intravenous and oral) with geometrical calculations of areas under the insulin-time curve [10,12,14]. This study however measured absolute concentrations of plasma insulin after an oral glucose load, a method also used by Haffner *et al.* [12] and the Bogalusa heart study workers [11]. Results reported by both methods consistently observed hyperinsulinaemia in offspring of diabetics.

Elevated plasma insulin responses reported are thought to reflect diminished insulin sensitivity (insulin resistance with a compensatory insulin response [10]). The significantly higher fasting plasma glucose levels also seen in this study, in concert with higher plasma insulin, suggests that the offspring of diabetics exhibit some degree of insulin resistance even though they were glucose tolerant.

This study therefore demonstrates hyperinsulinaemia in the offspring of Nigerian Type 2 DM patients, which is suggestive of insulin resistance. In Caucasians, Hispanics and Pima Indians, hyperinsulinaemia has been shown to predict progression to Type 2 DM later on in life [10,15]. This implies that they are at a greater risk for developing Type 2 DM. These findings are in support of the "insulin resistance pancreatic exhaustion" hypothesis of Type 2 DM, which states that as a result of chronic insulin resistance, compensatory hyperinsulinaemia develops to maintain glucose homeostasis, and that diabetes mellitus develops when pancreatic hypersecretion of insulin fails. The presence of identifiable metabolic abnormalities such as hyperinsulinaemia and a reduced glucose disposal rate may predict risk of Type 2 DM and thus have important implications for the primary prevention of Type 2 DM [15].

Further multiple regressional analysis showed that the differences in fasting plasma insulin and 2 hour post-glucose

load insulin observed were only accounted for by the presence of parental history of diabetes and were not influenced significantly by BMI, waist and hip circumferences. This emphasizes the strong influence of a positive family history of Type 2 DM (i.e., genetic influences) on insulin action [3,5,10].

Some limitations of this study must be mentioned. While fasting or stimulated plasma insulin measurements are simple to perform, it is necessary to remember that these measurements are only an indirect method of assessing insulin resistance. The oral glucose tolerance test with measurement of plasma insulin has limitations in that it has poor reproducibility even in those with normal glucose tolerance. In conclusion this study has shown that offspring of Nigerian Type 2 diabetics demonstrated significantly higher mean fasting and two hour post glucose load plasma insulin concentrations when compared with age and sex matched controls.

Bearing in mind the small sample size utilized in this work, larger prospective multicentre studies on offspring of diabetics are needed to help in identifing metabolic abnormalities that may precede and predict subsequent progression to Type 2 DM amongst offspring of Nigerian Type 2 diabetics. It would be desirable to have a long-term follow up of offspring of diabetics in this present study to see if they go on to develop diabetes mellitus.

There is a need to embark on health education strategies amongst offspring of non-insulin-dependent diabetics, directed towards lifestyle modification and measures aimed at prevention of Type 2 DM, especially in persons exhibiting markers known to be predictive of progression. Markers identified are hyperinsulinaemia, reduced glucose disposal rates and relatively higher fasting and 2-hour post-glucose load plasma glucose concentrations despite elevated fasting plasma insulin concentrations.

A high risk population approach to the primary prevention of Type 2 DM is suggested in view of the rising prevalence of Type 2 DM in Nigeria.

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