Int J Diabetes & Metabolism (2005) 13: 24-27

Insulin resistance in type 2 diabetic Nigerians.

Adamu G Bakari and Geoffrey C Onyemelukwe

Department of Medicine, Ahmadu Bello University and Ahmadu Bello University Teaching Hospital Zaria, Nigeria

Abstract

Background: Considerable interest has been generated and still continues on the role of insulin resistance in the aetiology of glucose intolerance and its complications. There is evidence to suggest that racial factors are important in this regard. Whereas Caucasian studies suggest insulin resistance to be universal in type-2 diabetes, African-American studies on the other hand suggest the contrary in a significant proportion of type-2 diabetic African-Americans. No previous study has been undertaken in this aspect in type-2 diabetic Nigerians. **Objective:** To measure insulin resistance using the Homeostasis Model Assessment (HOMA) among type-2 diabetic Nigerians. **Subjects and methods:** A cross sectional study involving 40 type-2 diabetic subjects and 36 controls. The HOMA method was used to compute insulin resistance for each subject. Individual HOMA scores were subjected to statistical analysis between the two (diabetic and non-diabetic) groups. **Results:** Forty type 2 diabetic patients and 36 healthy age and socio-economic status matched control subjects were studied. Mean HOMA scores were significantly higher among type 2 diabetic subjects than controls. Ten (27.8%) of the control subjects demonstrated HOMA insulin resistance values greater than one compared to 35 (87.5%) of type-2 diabetic patients ($p<0.05$). **Conclusion:** It is concluded although type-2 diabetic patients exhibit more insulin resistance than control subjects, insulin sensitive variants of type-2 diabetes is also found in this population.

Key words: *HOMA, Insulin resistance, type-2 diabetes, Nigerians*

Introduction

Type-2 diabetes mellitus is a heterogeneous disorder characterized by chronic hyperglycaemia due to dynamic interactions between varying defects of insulin secretion and insulin resistance. Either of these defects may be the predominant feature in a particular case.[1]

There is evidence to suggest that the underlying defect in type 2 diabetes varies from one population to another and even within populations. Martins *et al* [2] established that insulin resistance precedes and strongly predicts the development of type 2 diabetes mellitus among whites in the United States, Banerji and Lebovitz[3] on the other hand, noted that both insulin sensitive and insulin resistant forms of type 2 diabetes exist among African-American type 2 diabetic patients, with about 44 percent of such patients been insulin sensitive. More interestingly these observations were made even when type-2 diabetes was clinically manifest.

More recently, it has been shown that HOMA estimated insulin resistance is an independent predictor of cardiovascular disease in type-2 diabetic subjects.[4]

As opposed to the vast literature on insulin resistance among type 2 diabetic patients in technically advanced regions of the world, there is paucity of published material in Nigeria in particular and Africa in general. We report the first study on insulin resistance using the HOMA method in Nigerian type 2 diabetic patients.

Correspondence to: Dr. Adamu Girei Bakari, Consultant Physician & Endocrinologist., Department of Medicine, Ahmadu Bello University Teaching Hospital, Zaria, Nigeria. E-Mail: abgirei@yahoo.com, Phone: +2348037018639, Fax: +23469334126

Subjects and Methods

Type 2 diabetic patients attending the diabetic clinic of Ahmadu Bello University Teaching Hospital (ABUTH) Zaria, Nigeria, 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 if 6.7 to 7.8 mmol/L and or 2 HPP of 8.9 to 10.0 mmol/L)[5], 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 diabetics was however based on clinical grounds of non-dependence on insulin for survival.[6] The exclusion criteria were insulin dependence, evidence of secondary diabetes, current insulin therapy or previous history of ketosis, and pregnancy. Use of oral contraceptives and clinical or biochemical evidence of disease of the liver, kidney or thyroid were also exclusion criteria.

Thirty-six healthy, age, sex and socio economic status matched 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, current use of any form of medication and engagement in competitive sport; factors known to interfere with insulin secretion and action.

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 0.5 kg. Heights (in meters) 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.[7]

Metabolic studies
Oral hypoglycaemic agent therapy was withdrawn a week before metabolic studies to eliminate the effect of these drugs on insulin secretion.[6]

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. The plasma was then divided into aliquots for plasma glucose and insulin estimation. Aprotinin 200 KIU per ml of plasma[8] was added to the aliquot for insulin assay; this was kept at $^{-}20^{0}$Centigrade until analysis using a commercially available human insulin ELISA 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 % and 4.8% respectively, sensitivity of 99% for human insulin and no cross-reaction with pro-insulin. Plasma glucose analyses were done within an hour of collection of plasma using a glucose oxidase method. [9]

Insulin resistance values were derived using the homeostasis model assessment (HOMA) method,[10] employing the equation below.
Insulin resistance = $\frac{\text{(Fasting plasma insulin micro-units/L) X (Fasting plasma Glucose mmol/L)}}{22.5}$

The figure 22.5 in the equation brings the insulin resistance value to 1.0 (insulin sensitivity of 100 %) of 'normal' subjects.

Results are presented as mean ± standard deviation. Unpaired student's t-test was used to determine the differences between continuous variables while chi-square test was used for categorical variables. The level of statistical significance in each case was taken as $p \leq 0.05$.

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 subjects (P>0.5). Similarly, the sex distribution for the two groups was also similar (P > 0.5). Table 1 summarizes the characteristics of type 2 diabetic patients and control subjects. There were marked variations in the individual values of HOMA IR scores in both diabetic and non diabetic populations. However, despite a marked variation in individual HOMA scores, type-2 diabetic patients exhibited higher scores compared to control subjects. Mean HOMA IR among type-2 diabetic patients was 1.73 (range 0.4-7.6) while mean HOMA IR for control subjects was 1.11(range 0.19-6.4).

Ten (27.8%) of the control subjects demonstrated HOMA insulin resistance values greater than one compared to in 35 (87.5%) of type-2 diabetic patients. Similarly, seven (19.4%) of control subjects had HOMA IR scores of ≥ 2.0 compared to 16 (40%) of type-2 diabetic patients.

Discussion
The HOMA method developed in 1985 by Matthews and co-workers[10] was used in this study as it is simple and appropriate to developing countries where dynamic studies like the euglycaemic glucose clamp technique,[11] though the gold standard, may not be feasible due to the degree of sophistication and cost of equipment necessary.

The HOMA method utilizes single fasting plasma values of glucose and the corresponding fasting plasma insulin levels. The major shortcoming of the method is that the model utilizes values generated from lean young adults (less than 35 years old) of Caucasian origin as standard, against which subjects are compared. Values for older adults would probably be different from those documented for this younger group, as older individuals are known to be relatively more insulin resistant.[12] Furthermore, racial factors are known to be significant in the aetiology of insulin resistance[13]. Not withstanding these shortcomings, our findings would still be valid since the confounding effects of race and age are expected to be same among control subjects and type 2 diabetic individuals in this study; since ages in the two groups are similar and all subjects were drawn from the same racial and ethnic background. Recently, the HOMA method has been revalidated as a reliable method to assess insulin resistance in clinical practice as the HOMA IR score has been shown to closely mirror the insulin resistance values obtained by the euglycaemic glucose clamp technique in the assessment of insulin sensitivity.[14]

In our study, ten (27.8%) of the control subjects demonstrated HOMA insulin resistance values greater than one compared to 35 (87.5%) of type-2 diabetic patients. Since HOMA IR score of greater than one implies insulin sensitivity of less than 100% from the equation, this could imply insulin resistance. However, although a HOMA score of 1.0 is the ideal, the study of Bonora *et al*[14] found a mean HOMA IR score of 2.06 ± 0.14 in the normal non diabetic population. In the absence

Table 1: Characteristics of type-2 diabetic patients and control subjects studied.*

Parameter.	Type-2 diabetic patients. (n= 40)	Control subjects. (n= 36)	P Value
Mean Age (YEARS).	49.4 ± 9.7	48.6 ± 9.8	>0.5
Sex ratio (M/F).	2.3	2.0	>0.5
Mean BMI.(KgM^{-2}).	24.9 ±4.43	22.9 ± 4.02	<0.02
Mean WHR.	1.03 ± 0.08	0.92 ± 0.08	<0.01
Mean HOMA IR Score.	1.73 (0.4-7.6)	1.11 (0.19-6.4)	<0.05
Mean FPG (mmol/L)	9.77 ± 4.03	3.95 ± 0.98	<0.001
Mean Fasting plasma Insulin (micro-units per Ml)	4.20 ± 1.78	5.72 ± 2.16	<0.05

- Values in brackets represent ranges while values after the ± sign represent standard deviation from mean.
- FPG = Fasting plasma glucose.

of local reference data for HOMA IR score, we may assume a value of greater than 2.0 to represent insulin resistance. In this study seven (19.4%) of control subjects had HOMA IR scores of ≥ 2.0 compared to 16 (40%) of type-2 diabetic patients.

Our findings are similar to the findings of Reaven and co-workers who reported that 25 percent of normal individuals in the general European population are as insulin resistant as the diabetic population.[13] Our finding of HOMA IR >2.0 in about a fifth of normal controls in an African setting is worrisome as previous studies in the 1960s suggested that insulin sensitivity was virtually universal in the African.[15,16] Life style changes from the traditional African life style that was associated with a high intake of high fiber diets and high levels of physical exercise to meet up with day to day activities were thought to be the reasons for the then high levels of insulin sensitivity. Anecdotal evidence suggests that more and more people in this environment are opting for more refined foods and sedentary lifestyles, all dividends of urbanization. This could account for the high level of insulin resistance among the control subjects.

In the present study, type 2 diabetic individuals demonstrate significantly higher indices of insulin resistance than control subjects. However, the data in this study is based on cross sectional observations, and although they suggest that insulin resistance occurs significantly more in type 2 diabetic patients in Nigeria, it does not provide insight as to the temporal relationship between insulin resistance and the onset of type 2 diabetes. Hyperglycaemia, the hall mark of established type 2 diabetes is also known to induce and sustain insulin resistance making it impossible to distinguish defects of insulin secretion or action that are pathogenically involved in the development of type-2 diabetes and those that result from the effects of hyperglycaemia.[18,19] However, if insulin resistance precedes the onset of type 2 diabetes mellitus, this anomaly is expected to be found in a fraction of the non-diabetic population. This is supported by this study.

We conclude that insulin resistance occur in a good number of type 2 diabetic patients in this study, and in agreement with studies in African-American type 2 diabetic patients, some of our type 2 diabetic patients do not exhibit insulin resistance. Further prospective studies are required to establish the natural history of insulin resistance in this population.

References

1. World Health Organization. Definition, Diagnosis and classification of diabetes mellitus and its complications. Report of a WHO consultation, WHO; Geneva, 1999.
2. Martin BC, Warram JH, Krowleski AS, et al. Role of glucose and insulin resistance in the development of type 2 diabetes mellitus: results of a 25 year follow up study. Lancet 1992; 340:925-929.
3. Banerji MA, Lebovitz H. lnsulin sensitive and insulin resistant variants in NIDDM. Diabetes 1989; 38:784-792.
4. Bonora E F, Formentini G, Calcaterra F et al, HOMA estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona diabetes study. Diabetes Care 2002; 25:1135-1141.
5. Williams G. Management of non-insulin dependent diabetes mellitus. Lancet 1994; 343: 95-100.
6. Omar MAK, Asmal AC. Insulin responses to oral glucose in young African and Indian non- insulin dependent diabetic patients in Natal. Trop Geog Med 1983; 35:59-64.
7. World Health Organization Expert committee: Physical status; the use and interpretation of anthropometry. Report of a WHO expert committee. Technical report series 854, WHO Geneva, 1995.
8. Verstraete M. Clinical applications of inhibitors of fibrinolysis. Drugs 1985; 29: 236-261.
9. Trinder P. Determination of Glucose in blood using glucose-oxidase with an alternative oxygen acceptor. Ann Clin Biochem 1969; 6:24-27.
10. Matthews DJ, Hoskers JP, Rudenski AS, Waylur BA, Trencher DY, Turner RC Homeostasis model assessment Insulin resistance and β-cell function from

fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412-419.
11. Defronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol 1979; 237: E214-E223.
12. Defronzo RA Glucose intolerance of aging evidence for tissue insensitivity to insulin. Diabetes 1979; 28:1095-1 101.
13. Reaven GM, Hollenbeck CB, Chen YD. Relationship between glucose intolerance, insulin secretion, and insulin action in non obese individuals with varying degrees of glucose intolerance Diabetologia l989; 32:52-55.
14. Bonora E, Saggiani F, Targher G, et al. Homeostasis Model Assessment closely mirrows the glucose clamp technique in the assessment of insulin sensitivity. Diabetes Care 2000; 23:23-25.
15. Adadevoh BK. Endocrine pattern of the African: Clinico-Biochemical assessment Trop Geog Med 1970; 22:125-141.
16. Adadevoh BK, Emuruem DSC, Ihenacho HNC, et al. Tolerance to insulin by Nigerians. West Afr Med J 1968; 17:93-95.
17. Nagulesparan M, Savage PJ, Knowler WC, et al. Increased in vivo insulin resistance in non diabetic Pima Indiana compared with Caucasians. Diabetes, 1982; 31: 952-956.
18. Rosetti L, Glaccari A, Defronzo RA. Glucose toxicity. Diabetes Care 1990; 13:610-630.
19. Unger RH, Grundy S. Hyperglycaemia as an inducer of as well as a consequence of impaired islet cell function and insulin resistance: implications for the management of diabetes. Diabetologia 1985; 28:110-121.