

# Basal Insulin Resistance and Secretion in Nigerians With Type 2 Diabetes Mellitus

J.M. Oli, M.D.,<sup>1</sup> A.A. Adeyemo, M.D.,<sup>2</sup> G.O. Okafor, Ph.D.,<sup>1</sup> E.N. Ofoegbu, M.D.,<sup>1</sup> B. Onyenekwe, M.D.,<sup>1</sup> C.J. Chukwuka, M.D.,<sup>1</sup> C.N. Onwasigwe, M.D.,<sup>1</sup> S. Ufelle, M.Sc.,<sup>1</sup> G. Chen, M.D.,<sup>2</sup> and C.N. Rotimi, Ph.D.<sup>2</sup>

## Abstract

**Aim:** The objective of this study was to estimate basal insulin resistance (IR) and insulin secretion (IS) in Nigerians with type 2 diabetes mellitus (T2DM).

**Methods:** The homeostasis model assessment (HOMA) method was used to estimate basal IR and IS in 146 Nigerians with T2DM and in 33 controls at the University of Nigeria Teaching Hospital (UNTH), Enugu, Nigeria. Correlations and multiple regression analysis between Box–Cox-transformed IR and log-transformed IS and anthropometric indices were carried out.

**Results:** IR and reduced IS were present, respectively, in 139 (95.5%) and 109 (74.7%) of the diabetic subjects and in 25 (75.8%) and 4 (12.1%) of the controls. In the diabetic subjects, age at diagnosis, duration of diabetes, waist circumference (WC), and body mass index (BMI) correlated significantly with IR ( $r = -0.2399$ ,  $P = 0.0035$ ;  $r = 0.1993$ ,  $P = 0.0166$ ;  $r = 0.2267$ ,  $P = 0.0059$ ;  $r = 0.2082$ ,  $P = 0.0120$ ; respectively), whereas duration of diabetes, WC, and BMI correlated significantly with IS ( $r = -0.2166$ ,  $P = 0.0091$ ;  $r = 0.3062$ ,  $P = 0.0002$ ;  $r = 0.2746$ ,  $P = 0.0008$ ; respectively). Age at diagnosis, WC, and duration of diabetes were significant predictors of IR ( $\beta = -0.0161$ ,  $P < 0.001$ ;  $\beta = 0.0121$ ,  $P = 0.002$ ;  $\beta = 0.0138$ ,  $P = 0.042$ ; respectively), whereas duration of diabetes and WC significantly predicted IS ( $\beta = -0.0159$ ,  $P = 0.025$ ;  $\beta = 0.0155$ ,  $P < 0.001$ ).

**Conclusions:** This study shows that both IR and reduced IS are major features of T2DM in Nigerians and that WC consistently correlated and predicted IR. WC measurement is simple and ideal in resource-poor settings for the detection of IR and abdominal obesity. The apparent rarity of coronary heart disease (CHD) in black Africans with T2DM despite a high prevalence of IR warrants further investigation.

## Introduction

IT IS WIDELY ACCEPTED THAT in many populations that insulin resistance (IR) and reduced insulin secretion (IS) are major features of type 2 diabetes mellitus (T2DM), with features ranging from predominantly IR with relative insulin deficiency to predominantly IS defect.<sup>1,2</sup> Both dysfunctions are usually present by the time T2DM is established.<sup>3</sup> Although there is increasing prevalence of T2DM in sub-Saharan African populations, sometimes with atypical presentations and mechanisms,<sup>4</sup> there are limited data to show if these features apply to Africans with T2DM. In most other populations, IR is an independent risk factor for cardiovascular diseases such as coronary heart disease (CHD) in people with T2DM,<sup>5,6</sup> and yet CHD is rare in black Africans with and without T2DM.<sup>7,8</sup>

Therefore, we have estimated basal IR and IS in a group of Nigerians with T2DM to determine if IR and reduced IS are significant features of T2DM in a sub-Saharan African population. We also measured simple anthropometric indices that have been found to correlate well with and predict IR in most other populations<sup>9–11</sup> and related them to IR in our subjects.

## Patients and Methods

This cross-sectional study was carried out at the University of Nigeria Teaching Hospital (UNTH), Enugu, Nigeria. The Ethics Committee of the Hospital approved the study, and informed consent was obtained from each subject. T2DM subjects who had been attending the Diabetes

<sup>1</sup>College of Medicine, University of Nigeria, Enugu Campus, Enugu, Nigeria.

<sup>2</sup>National Human Genome Center, Department of Community Health and Family Practice, Howard University, Washington, D.C.

Clinic of the UNTH, Enugu, Nigeria, and who satisfied the following criteria were recruited for the study: (1) A diagnosis of T2DM based on fasting blood glucose (FBG) of  $\geq 126$  mg/dL (7.0 mmol/L) or random blood glucose of  $\geq 200$  mg/dL (11.1 mmol/L) on 2 separate occasions or justified pharmacological treatment for T2DM, (2) age 35 years or more at the time of diagnosis, (3) not requiring insulin nor having been treated with insulin within the first year of diagnosis and not on insulin at the time of the study, and (4) no recorded episodes of ketonuria. The detection of autoantibodies to glutamic acid decarboxylase (GAD) was used to exclude probable cases of type 1 diabetes mellitus (T1DM). A total of 146 diabetic subjects who satisfied the above criteria were recruited for the study; 33 normal subjects who were spouses of some of the diabetic subjects were recruited as controls. The controls had FBG of 6.1 mmol/L or less, as determined on 2 different occasions.

All subjects were studied after an overnight fast of at least 8 h on the night preceding the clinic visit for the study. Fasting venous samples were obtained from each subject for the measurement of glucose and insulin. Glucose assay was performed using an automated enzymatic system, the Abbot Spectrum multichromatic analyzer (Abbott Laboratories, Abbot Park, IL), with a coefficient of variation (CV)  $< 3.0\%$ . Insulin assays were performed by double-antibody radioimmunoassay developed in the centralized reference laboratory at the Diabetes Endocrinology Research Center Immunoassay Core Laboratory in Seattle, Washington. The interassay CV for the insulin assay was  $< 6.9\%$ .

Data collected on each subject included: Age at onset of T2DM, duration of T2DM in years (for diabetic subjects), height and weight (for BMI calculation), and waist and hip circumferences. Height (meters) was measured with a stadiometer with the subject standing in light clothing and without shoes. Weight was measured to the nearest 0.1 kg using a digital electronic scale. Waist and hip circumferences were measured to the nearest 0.1 cm twice in each subject and the average used for waist-to-hip ratio (WHR) calculations.

IR and IS were estimated with homeostasis model assessment (HOMA).<sup>11</sup> IR was defined as the product of fasting serum insulin ( $\mu\text{U/mL}$ ) and FBG (mmol/L) divided by 22.5, whereas IS was defined as the product of 20 and fasting

insulin ( $\mu\text{U/mL}$ ) divided by FBG (mmol/L)  $-3.5$ . An IR of  $\geq 2$  was used in this study to define individuals with IR, whereas an IS score of  $< 100$  defined those with reduced IS. The IR cutoff point approximates to the mean value of  $1.95 + 1$  standard deviation (SD) (0.1) obtained in Ghanaians with normal FBG and blood pressure using the HOMA model.<sup>12</sup> Obesity was defined as high body mass index (BMI) ( $\geq 30$  kg/m<sup>2</sup>) and/or high WHR ( $> 0.90$  in men,  $> 0.85$  in women).<sup>13</sup> Because both IR and IS values were not normally distributed, they were transformed to normality using a Box-Cox transformation (IR) or a log transformation (IS). Correlations between the transformed IR, IS, and continuous variables were estimated using the Pearson rank correlation coefficient. The chi-squared test was used to analyze contingency tables of categorical variables. Multiple linear regression models were used to estimate how well the variables could predict those with IR and reduced IS. The models had either IR or IS as the outcome variable and age, sex, duration of T2DM, BMI, WC, and WHR as predictors. A *P* value of  $< 0.05$  was considered statistically significant. The statistical analyses were done using Stata version 8 (Stata Corp, College Station, TX).

## Results

A total of 146 diabetic subjects (73 females and 73 males) with mean age  $53.6 (\pm 10.02)$  years at diagnosis were studied. The characteristics of the T2DM subjects and controls are shown in Table 1. IR was present in 139 (95.2%) of the diabetic subjects, whereas IS was reduced in 109 (74.7%). The mean IR in the subjects was  $9.4 (\pm 12.9)$  and IS was  $112.6 (\pm 79.6)$ . Obesity was present in 124 (84.9%) of the subjects accounted for by mainly abdominal obesity (high WHR), which was present in 103 (83.1%) subjects. No gender differences were found in terms of IR (*P* = 0.842) and IS (*P* = 0.871). Sixteen (22%) of the 73 males had a WC of  $> 102$  cm and 46 (63%) of the 73 females had WC of  $> 88$  cm. Thus, 66 of the 146 subjects (42.5%) had high WC measurements.

The small number of spousal controls consisted of 33 subjects, 7 males (21.2%) and 26 females (78.8%), with mean age of  $45.7 (\pm 8.7)$  years. IR was present in 25 (75.8%) of the controls, whereas IS was reduced in 4 (12.1%). Mean IR and IS were  $3.4 (\pm 2.8)$  and  $173.5 (\pm 113.7)$ , respectively. Obesity

TABLE 1. CHARACTERISTICS OF THE T2DM SUBJECTS AND CONTROLS

	Number (%)		<i>P</i> value
	T2DM subjects <i>n</i> = 146	Controls <i>n</i> = 33	
Gender (number [%] male)	73 (50%)	7 (21%)	0.003 <sup>a</sup>
Age (mean $\pm$ SD) years	53.6 (10.0)	45.7 (8.7)	$< 0.0001^a$
Prevalence of IR	139 (95.2%)	25 (75.8%)	$< 0.0001^a$
Prevalence of reduced IS	109 (74.7%)	2 (12.1%)	$< 0.0001^a$
IR (mean $\pm$ SD)	9.4 ( $\pm 12.9$ )	3.4 ( $\pm 2.8$ )	$< 0.001^a$
IS (mean $\pm$ SD)	112.6 ( $\pm 79.6$ )	173 ( $\pm 113.7$ )	$< 0.001^a$
Obesity	124 (84.9%)	21 (53.6%)	0.005 <sup>a</sup>
Mean BMI ( $\pm$ SD)	25.6 (4.4)	26.9 (4.77)	0.11

<sup>a</sup>*P*  $< 0.05$ .

Abbreviations: T2DM, type 2 diabetes mellitus; SD, standard deviation; IR, insulin resistance; IS, insulin sensitivity; BMI, body mass index.

was present in 21 (63.6%). Only 1 of the 7 males (14.3%) had a WC of >102 cm and 17 of the 26 females (65.4%) had a WC of >88 cm. Thus, 18 of the 33 controls (54.5%) had a high WC. There was no statistically significant gender difference in any of the variables, including IR and IS. The 75th quartile IR value for the controls was 4.1 and the 25th quartile IS value was 117.1.

The T2DM subjects and controls differed significantly in gender ( $P = 0.003$ ), age ( $P < 0.0001$ ), prevalence of IR and IS, respectively ( $P < 0.001$ ,  $P < 0.001$ ), mean IR ( $P < 0.001$ ), mean IS ( $P < 0.001$ ), and obesity ( $P = 0.005$ ) (Table 1). The diabetic subjects had higher WHRs than the controls ( $P < 0.001$ ), but there was no significant difference in terms of WC ( $P = 0.7344$ ) and BMI ( $P = 0.11$ ) between diabetic subjects and the controls.

Table 2 shows some of the variables and their coefficients among the 146 diabetic subjects. Age at diagnosis of DM, duration of DM, WC, and BMI showed low but significant correlations with IR ( $r = -0.2399$ ,  $P = 0.0035$ ;  $r = 0.1993$ ,  $P = 0.0166$ ;  $r = 0.2267$ ,  $P = 0.0059$ ;  $r = 0.2082$ ,  $P = 0.0120$ ; respectively), whereas duration of diabetes, WC, and BMI correlated significantly with IS ( $r = -0.2166$ ,  $P = 0.0091$ ;  $r = 0.3062$ ,  $P = 0.0002$ ;  $r = 0.2746$ ,  $P = 0.0008$ ; respectively).

Age at diagnosis of diabetes, WC, and duration of diabetes were significant predictors of IR ( $\beta = -0.0161$ ,  $P < 0.001$ ;  $\beta = 0.0121$ ,  $P = 0.002$ ;  $\beta = 0.0138$ ,  $P = 0.042$ ; respectively), whereas duration of diabetes and WC significantly predicted IS ( $\beta = -0.0159$ ,  $P = 0.025$ ;  $\beta = 0.0155$ ,  $P < 0.001$ ). On stepwise multiple linear regression analyses, age, WC, and duration of T2DM were significant independent predictors of IR, whereas the latter 2 (WC and duration of T2DM) were significant independent predictors of IS (Table 3).

## Discussion

There are relatively scanty data on the prevalence of IS and/or IR in T2DM in West Africa. This study showed that, using our cutoff points, there is a high prevalence of IR (95.2%) and reduced IS (74.7%) among Nigerians with

T2DM. Therefore, both IR and reduced IS are major features of established T2DM in Nigerians. Additionally, the study showed that WC measurement is the most consistent, simple anthropometric parameter that correlated and predicted IR in the patients.

It is usually recommended that IR in a population be defined by the 75th percentile of HOMA-IR index from that population, because of differences in body sizes.<sup>13</sup> Unfortunately we do not have such a value for Nigerian or black African populations. Our number of controls in this study was not large or representative enough to estimate such a value for our population. Therefore, we have used an IR cutoff level of  $\geq 2$  to define IR in our study population on the basis of an approximation to the mean + 1 SD value obtained in Ghanaians with normal FBG and blood pressure using the HOMA model.<sup>12</sup> However, it should be noted that the mean HOMA-IR for normal subjects in most populations is between 2.1 and 2.7.<sup>14</sup> Specific cutoff points used for the definition of IR in some European and African populations range from 1.62 to 2.77.<sup>15-19</sup> Our cut off point of  $\geq 2$  for defining IR in this study falls within the range of these values and also within the confidence interval of 1.76–2.03 (mean 1.89) for adults of African origin living in England.<sup>20</sup> Using the upper limit of >2.77 of the range as the cutoff point, 87% of our patients would have IR, which is similar to about 85% reported for most T2DM populations.<sup>14</sup> The lowest cutoff point of 1.62 would have 97.3% or virtually all our patients with IR. The cutoff point of 4.1 (75% percentile for our controls) would have 72% of our patients with IR. These figures suggest that the majority of Nigerians with T2DM may have IR. Our mean IR value of 9.4 in Nigerians with T2DM in this study is also within the 8.3–9.5 range for T2DM subjects reported from other populations.<sup>14</sup> This further justifies the fact that IR is a feature in our patients with T2DM. We are not aware of any published data on the prevalence of IR in black Africans with T2DM. Clearly large studies of IR in nondiabetic black African populations are indicated to establish the normal reference values or cut off values for IR to make epidemiological and comparative analysis of IR more meaningful.

BMI and WC, but not WHR, correlated with IR in our study. Additionally, WC was the only measurement that consistently correlated with and predicted IR. This is similar to the findings that WC is indeed a better anthropometric predictor of many constituents of MS such as IR in many populations,<sup>21-24</sup> including black South Africans.<sup>25</sup> A most recent study has indeed emphasized WC as a strong independent risk factor for IR.<sup>26</sup> In this study, 42.5% of the diabetic subjects (63% of the females and 22% of the males) had high WC and therefore central or abdominal obesity similar to 46% (75% females and 17% males) found in West Indians with T2DM.<sup>27</sup> Measurement of WC in subjects with T2DM is a simple key tool, devoid of complicated calculations and measurements (such as for WHR and BMI) for the detection of abdominal obesity and possibly IR. Such measurements can be carried out at primary health levels, even by semiliterate staff in poor-resource settings in sub-Saharan Africa.

From our data, a high percentage of our patients with T2DM have IR, which in most other populations is usually strongly associated with a high risk of CHD. Yet, presently, there is this apparent paradox of a comparatively low prevalence of CHD in the general and diabetic populations of sub-Saharan Africa.<sup>7,8</sup> It may be that IR has a different clinical

TABLE 2. CORRELATIONS BETWEEN IR, IS, AND SELECTED VARIABLES IN THE 146 T2DM SUBJECTS

	Pearson <i>r</i> ( <i>P</i> )	
	IR	IS
Age at diagnosis (years)	<b>0.2399</b> (0.0035 <sup>a</sup> )	-0.0059 (0.9432)
Duration of T2DM (years)	<b>0.1993</b> (0.0166 <sup>a</sup> )	<b>-0.2166</b> (0.0091 <sup>a</sup> )
WC	<b>0.2267</b> (0.0059 <sup>a</sup> )	<b>0.3062</b> (0.0002 <sup>a</sup> )
BMI	<b>0.2082</b> (0.0120 <sup>a</sup> )	<b>0.2746</b> (0.0008 <sup>a</sup> )
WHR	0.1502 (0.0703)	0.1186 (0.1541)

Significant correlations in are in boldface.

<sup>a</sup> $P < 0.05$ .

Abbreviations: IR, insulin resistance; IS, insulin sensitivity; T2DM, type 2 diabetes mellitus; WC, waist circumference; BMI, body mass index; WHR, waist-to-height ratio.

TABLE 3. SIGNIFICANT PREDICTORS OF IR AND IS IN NIGERIAN T2DM SUBJECTS ON STEPWISE MULTIPLE LINEAR REGRESSION

Outcome	Significant covariate	$\beta$	SE ( $\beta$ )	P	Model $r^2$
IR	Age at diagnosis T2DM	-0.0161	0.004	<0.001	
	WC	0.0121	0.003	0.002	14.1%
	Duration T2DM	0.0138	0.007	0.042	
IS	Duration T2DM	-0.0159	0.007	0.025	
	WC	0.0155	0.004	<0.001	11.8%

Abbreviations: IR, Box-Cox-transformed HOMA insulin resistance index; HOMA, homeostasis model of assessment; IS, log HOMA insulin sensitivity index; T2DM, type 2 diabetes mellitus; WC, waist circumference.

connotation in the African diabetic population. It is usually unclear to what extent IR of T2DM could be explained by other abnormalities associated with the diabetes. It is known that glucotoxicity contributes to IR in T2DM.<sup>28</sup> Glucotoxicity induced by chronic hyperglycemia from inadequate diabetes treatment and delayed diagnosis of DM due to poor socioeconomic situation are likely to be more common in resource-poor settings such as in Nigeria. Therefore, it may be that under such settings there is a greater contribution to IR from glucotoxicity more than from obesity and other factors that traditionally contribute to IR and CHD. For instance, African diabetic patients tend to have a less atherogenic lipid profile than Caucasians.<sup>29</sup> Studies are clearly indicated in black African populations to show why CHD is comparatively uncommon in black Africans with T2DM despite a high prevalence of IR in the patients.

Age at diagnosis correlated negatively with and predicted IR in our study, similar to the findings in another study.<sup>30</sup> Duration of diabetes positively correlated with and predicted IR. This is contrary to the negative correlation with IR noted in the above study.<sup>30</sup> We postulate that chronic glucotoxicity that contributes to IR could provide a potential explanation for our observation because the chronicity of hyperglycemia due to poor metabolic control is time dependent and also more likely to occur under poor socioeconomic conditions of sub-Saharan Africa.

We have used the cutoff level of <100 HOMA to define those with reduced IS (74.7%). This cutoff level may not be satisfactory for definition purposes. However, the 25th percentile value for the controls was 117, and using this value would further increase the number of patients with reduced IS. In a recent study in which we assessed  $\beta$ -cell function in Nigerians with T2DM using glucagon stimulated C-peptide, we found that 51% had a value of  $\leq 1.8$  ng/mL, a level often regarded as severe enough for potential insulin requirement.<sup>31</sup> Therefore, reduced IS seems to be a feature of established T2DM in Nigerians. In this study, duration of diabetes negatively correlated and predicted IS, which is similar to the generally accepted view that  $\beta$ -cell function declines with duration of diabetes in T2DM.<sup>32</sup> WC and BMI positively correlated with IS in our study. Thus, the leaner the patient, the poorer the insulin secretion. This highlights the greater likelihood of lean T2DM patients being insulin-requiring.<sup>33</sup>

The comparison between the diabetic subjects and the controls shows some expected differences, although the small number of controls limits the inferences that can be drawn. There was no difference in BMI between the diabetic subjects and controls similar to findings in Ghanaians.<sup>34</sup> Interestingly,

IR was present in a high percentage (75.8%) of controls, whereas reduced IS was present in a small percentage (12.1%) of controls. This suggests that reduced IS may be more discriminatory than IR between the diabetic subjects and controls. The high prevalence of IR in both the diabetic subjects and the controls indicates that lifestyle modifications and therapeutic measures that ameliorate IR are also likely to be effective in the treatment and prevention of T2DM in black Africans.

This study has some limitations. First, the HOMA index only represents surrogate measures of IS and IR. Second, a single insulin measurement was used in this study instead of 3 samples taken at 5-min intervals.<sup>35</sup> Although the number of control subjects was small, we feel that the use of spouses as controls was advantageous because it could have minimized the possible influences of both genetic and environmental factors, which play some roles in IR and IS. This will highlight the true prevalence of IR and IS in the controls undiluted by these factors. The significant preponderance of females in the controls may have affected the results, although it has been found that visceral adipose tissue and glucose disposal are independent of gender in black T2DM patients.<sup>36</sup> A larger study designed to take these factors into consideration is needed to clarify the prevalence and role of IR and reduced IS in T2DM in black African populations.

In conclusion, this study shows that both IR and reduced IS are major features of T2DM in Nigerians and that WC best correlated and predicted IR in the subjects. In resource-poor settings, measurement of WC in subjects with T2DM is a simple key tool for the detection of abdominal obesity and IR. However, the apparent rarity of CHD in black Africans with T2DM, despite a high prevalence of IR, warrants further investigation.

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Address correspondence to:  
J.M. Oli, M.D.

Department of Medicine  
University of Nigeria Teaching Hospital  
Enugu  
Nigeria

E-mail: johnnieoli@hotmail.com

