Insulin resistance and cardiovascular risk in older adult Nigerians with type 2 diabetes

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ABSTRACT
Background: Insulin resistance (IR), which refers to decreased metabolic response to normal concentrations of insulin, has been associated with increasing age and is a trigger to the cascade of cardiometabolic abnormalities hence increasing cardiovascular disease (CVD) risk in elderly populations with type 2 diabetes (T2D). Strategies targeting IR may be key to mitigating excess CVD morbidities in elderly patients with T2D.

Aim: The aim of this study is to evaluate the relationship between IR and CVD and also to identify cardiometabolic risk (CMR) factors as primary targets of CVD reduction in the older populations of Nigerians with T2D.

Settings and Design: Lagos, Nigeria. Cross-sectional, analytical.

Subjects and Methods: A total of 363 adult Nigerians with T2D aged between 40 and 100 years old were consecutively recruited for this study. T2D was defined according to the WHO criteria. Data were collected using a questionnaire and fasting blood samples were collected for analysis.

Statistical Analysis Used: The data were analyzed using the IBM SPSS statistical package. Statistical significance was set at value of $P < 0.05$.

Results: T2D patients in the age group of 60–80 years had significantly higher blood pressure than those in the younger age group, ($P = 0.009$). Fasting plasma glucose (FPG) and glycated hemoglobin were the highest in the age group of 40–60 years, ($P = 0.016$). IR was associated with older age in the T2D ($P = 0.026$). IR showed a significant correlation with CMR factors. Multivariate regression showed FPG to be independently associated with IR ($P = 0.003$).

Conclusion: IR correlated with CMR factors and was independently associated with FPG, re-emphasizing focus on short-term blood glucose control in elderly diabetic populations.

Keywords: Cardiometabolic risk, cardiovascular disease risk, insulin resistance, type 2 diabetes

Introduction

Insulin resistance (IR) is defined as a reduction in the rate of glucose disposal elicited by a given insulin concentration. IR has been implicated in the pathogenesis of many metabolic diseases associated with aging including metabolic syndrome with its associated increased cardiometabolic risk (CMR) of dyslipidemia, dysglycemia, hypertension, and obesity.[12] It is also the first in the spectrum of metabolic aberrations leading to type 2 diabetes (T2D) and its cardiovascular complications.[2]
Aging has been associated with a decline in many if not all physiological functions of the body and a decline in carbohydrate handling are one of its hallmarks.[3] Elderly people are less glucose tolerant as manifested by a decline in glucose-mediated B-cell insulin release and deficient insulin-mediated skeletal muscle glucose disposal, describing a state of reduced insulin sensitivity and IR.[4,5]

The mechanism of age-related IR is not yet completely clear.[6] The interaction of many factors associated with aging likely contributes to the alteration of glucose tolerance in this population.[6] These factors include increased adiposity, decreased physical activity and decreased lean muscle mass,[7] insulin secretory defects and decreased hepatic sensitivity to insulin's action in suppressing glucose output, all of which occur with advancing age.[5,8]

Diabetes is an independent risk factor for cardiovascular disease (CVD).[9,10] CVDs are listed as the cause of death in approximately 65% of persons with diabetes.[11] Persons with diabetes are living longer and are vulnerable to the traditional microvascular and macrovascular complications of diabetes. Elderly adults with diabetes have a high prevalence of coronary heart disease[12] IR and chronic hyperglycemia increase CVD risk in T2D.[13]

T2D in older adults is a heterogeneous disease with distinctions made between prevalent disease which starts in middle age or earlier and incident diabetes, with onset at >65 years. These two, presenting with different clinical features, add to the complexity of a generalized screening and treatment recommendations for T2D.[1] Furthermore, health-care access and demographic variables account for racial and ethnic disparities[15] and hence that applications of findings from different regions will optimize care and improve treatment outcomes. This study will evaluate the relationship between increasing age, IR and CVD with an aim to identify CMR factors independently associated with IR which will be targets of cardiovascular risk reduction in the older population of Nigerians with T2D.

**Subjects and Methods**

During August 2016 and March 2017, 363 adult Nigerians with T2D aged between 40 and 100 years old were consecutively recruited into a cross-sectional, analytical study, from endocrinology clinics in tertiary and general hospitals in Lagos, Nigeria. T2D was defined according to the WHO criteria[16] and the patients were on treatment with oral hypoglycemic agents (mainly biguanides and sulfonylureas), anti-hypertensives and statins. Patients who were functional and cognitively intact were recruited into the study. Patients not ambulant, pregnant women and hospitalized patients were excluded from the study. Eligible study participants were counseled on the objectives of the study and the study protocol. The study was conducted according to the guidelines laid down in the Declaration of Helsinki and the Institutional Review Board of the University of Lagos approved the protocol. Informed consent from each participant who then completes an interviewer-administered, anonymous, standardized, and questionnaire. Participants then underwent anthropometric measurements and blood pressure (BP) measurements. The study participants reported on the morning of the study after an overnight (10–12 h) fast.

Venous blood was collected for fasting glucose, lipid profile, glycated hemoglobin (HbA1c), and insulin measurements. An ion-exchange chromatographic-spectrophotometric method for HbA1c was used on the point-of-care analyzer (Fortress Diagnostics, UK).

Fasting glucose and lipid profile were estimated from lithium heparin plasma on biochemistry autoanalyzer, Cobas C311 (Roche Diagnostics GmbH D-68298 Mannheim Germany). Fasting insulin was determined from serum using reagents from Biovendor Laboratories, (62100 Brno, Czech Republic) by an enzyme-linked immunoassay technique on Acurex Plate Read (Acurex Diagnostics, Ohio, USA, 419-872-4775).

IR was assessed using homeostatic model assessment of IR (HOMA-IR), HOMA IR-β (HOMA-B), quantitative insulin sensitivity check index (QUICKI), and fasting glucose-insulin ratio (FGIR) and calculated thus: HOMA-IR = fasting insulin (μIU/ml) × fasting glucose (mmol/L)/22.5[17] HOMA-%B = fasting insulin (μIU/ml) × 100/fasting glucose (mmol/L)[18] QUICKI = 1/[log (Insulin μU/mL) + log (glucose mg/dL)][19] FGIR = fasting glucose (mmol/L) × fasting insulin (μIU/ml).[20]

**Statistical analysis**

The data were analyzed using the IBM SPSS version 20.0 (SPSS Inc., Chicago, IL). The Chi-squared test, ANOVA, independent Student’s t-test, and Pearson’s correlation were employed for the analysis. Statistical significance was set at \( P < 0.05 \).

**Results**

Three hundred and sixty-three patients with T2D participated in the study, 33.6% were male and 66.4% were
female. The age range was 40–98 years with a mean of 59.07 ± 9.67 years. The study participants were divided into three age groups as follows: group 1 was aged 40–60 years, Group 2 was 61–80 years, and Group 3 was 81–100 years.

Table 1 shows the sociodemographic data of the study participants. The sociodemographic characteristics of the study participants were evaluated by gender, place of residence, tribal, educational level, and duration of T2D. Gender, place of residence, and tribe were evenly distributed across all three age groups, showing no statistically significant differences between groups.

The study participants differed significantly in their levels of education and duration of T2D. Almost 50% of the participants in Group 3 aged between 81 and 100 years had no education or had only a primary education compared with about 70% of participants in Group 1, aged between 40 and 60 years who had secondary school education or higher. The age group of 61–80 years had about equal proportions of individuals who had primary education or less and those who had secondary education or higher. The duration of T2D increased gradually along with increasing age across the three age groups, with 5.2% compared with 13.1% and 28.6% having over 15 years of T2D duration. Conversely, 68.9% of the study subjects in the first age group, compared to 47.7% and 14.3% in the second and third age groups, had T2D duration of <5 years.

Table 2 shows the characterization of CMR factors of study participants with T2D, along with mean values for hypertension, abdominal obesity, glycemic control, and dyslipidemia.

Along these lines, mean values for systolic BP, fasting plasma glucose (FPG) and HbA1c differed significantly between the three age groups of the study participants. The study participants in Group 2 aged 61–80 years had significantly higher mean systolic BP than the younger age group of between 40 and 60 years. Fasting glucose and HbA1c rose progressively across all three groups and were significantly higher in the youngest age group compared to that of the older groups. Lipid profile values were comparable in all three groups.

Table 3 compares the markers of IR; FGIR, HOMA-IR, HOMA-B, and QUICKI in the study participants aged 60 years or greater in the study participants with T2D.

FGIR was significantly higher in the age group <60 years with higher measures of FGIR, indicating higher values of IR. When different markers of IR were compared between age groups, FGIR was able to distinguish the presence and

Table 1: Sociodemographic data of the study participants with type 2 diabetes by gender, place of residence, tribal, educational level, and duration of type 2 diabetes

| Sociodemographic variables | Age groups (years) (%) |  |  |
|---------------------------|------------------------|--|---|
| Gender                    | Group 1: 40-60 (n=217; 59.8) | Group 2: 61-80 (n=139; 38.3) | Group 3: 81-100 (n=7; 1.9) |
| Males (n=118)             | 66 (32.8)              | 48 (33.6)                  | 4 (57.1)                  |
| Females (n=233)           | 135 (57.9)             | 95 (66.4)                  | 3 (42.9)                  |
| Place of residence        |                        |                           |                           |
| Urban (n=126)             | 81 (37.3)              | 44 (31.7)                  | 1 (14.3)                  |
| Rural (n=237)             | 136 (62.7)             | 95 (68.3)                  | 6 (85.7)                  |
| Tribe                     |                        |                           |                           |
| Yoruba (n=247)            | 143 (57.9)             | 98 (39.7)                  | 6 (2.4)                   |
| Igbo (n=60)               | 33 (55)                | 27 (45)                   | 0 (0)                     |
| Others (n=39)             | 19 (48.7)              | 19 (48.7)                  | 1 (2.6)                   |
| Level of education        |                        |                           |                           |
| Not educated (n=46)       | 25 (12.5)              | 18 (13.4)                  | 3 (42.8)                  |
| Primary (n=94)            | 44 (22.2)              | 49 (36.6)                  | 1 (14.3)                  |
| Secondary (n=108)         | 65 (32.8)              | 41 (30.6)                  | 2 (28.6)                  |
| Tertiary (n=90)           | 64 (45.5)              | 26 (19.4)                  | 1 (14.3)                  |
| Duration of T2D (years)   |                        |                           |                           |
| <5                       | 133 (68.9)             | 62 (47.7)                  | 1 (14.3)                  |
| 6-10                     | 35 (18.1)              | 34 (26.2)                  | 3 (42.8)                  |
| 11-15                    | 15 (7.8)               | 17 (13.1)                  | 1 (14.3)                  |
| >15                      | 10 (5.2)               | 17 (13.1)                  | 2 (28.6)                  |

*Statistically significant. T2D - Type 2 diabetes
absence of IR in adults who were <60 years of age and those who were older.

Table 4 shows the correlation of FGIR on CMR factors of hypertension, abdominal obesity, glycemic control, and dyslipidemia in older adults with T2D.

The CMR factors of diastolic BP, waist circumference (WC), FPG and HbA1c showed positive and statistically significant correlation with FGIR. After correcting for the duration of T2D and level of education, FGIR showed significant correlation with of diastolic BP, WC, FPG, and HbA1c.

Table 5 shows the multivariate regression of FGIR on CMR factors of diastolic BP, WC, FPG, and HbA1c in older adults with T2D.

The CMR factors which showed significant correlation with FGIR were put in a multivariate regression model with FGIR. When the CMR factors that were significantly associated with FGIR in the univariate analysis where put in a multivariate model, multivariate regression showed FPG to be independently associated with IR, \( P = 0.003 \).

**Discussion**

IR is associated with cardiovascular risk in older adult Nigerians with T2D through the mechanism of poor short-term blood glucose control.

Diabetes in older adults has been linked with increased morbidity. A study by Kirkman et al., reported that older adults with diabetes have an increased risk for both microvascular and cardiovascular complications of the disease.\(^{[14]}\) A review of current literature by Barzilay et al.,\(^{[21]}\) which evaluated risk factors for CVD risk in the elderly reported increased CVD risk with age in T2D. Among other findings, the review also noted that when the participants were classified based on blood glucose levels into normal, impaired glucose and diabetic, the highest incidence of CVD events occurred
in diabetics with the highest blood glucose levels.\textsuperscript{[21]} This compares to findings from multivariate regression from this study which returned fasting blood glucose to be independently associated with IR and CVD risk in older adults with T2D.

In this study, older adults with T2D, in Group 2, and aged 61–80 years had more CMR factors compared younger individuals in age Group 1, aged between 40 and 60 years. In this study, individuals in the oldest age group 80–100 years had the least levels of CMR factors. Some authors have reported higher CVD with increasing age,\textsuperscript{[21]} but subgroup analysis from a meta-analysis\textsuperscript{[22]} reported that when compared to nondiabetic controls, individuals with T2D older than 70 years, had lower values for CVD risk compared to younger age groups with diabetes. Summarizing the evidence, Barzilay et al.,\textsuperscript{[21]} concluded that there exits significantly increased risks of mortality and CVD among elderly individuals with T2D, although the heightened incidence of these outcomes appears less pronounced than in middle-aged cohorts. Worthy of note, however, is the low numbers of individuals aged between 80 and 100 years old recruited into the study which may bias outcome.

Although the American Diabetes Association guidelines on treatment targets for hyperglycemia in older adults, focuses on individualized therapy and ranges from HbA1c values of between 7.5% and 8.5% depending on presence other co-morbidities,\textsuperscript{[23]} our finding of short and long term glucose control being significantly higher in the youngest age group may also be contributed to by social factors such as this working age group not having sufficient time to access care.\textsuperscript{[24]}

FGIR was the surrogate marker of IR able to detect significantly higher levels of IR in T2D subjects 60 years and over compared to those <60 years of age, decreasing values of FGIR indicating higher levels of IR. T2D subject ≥60 years of age benefitted most from lifestyle interventions of the Diabetes Prevention Program,\textsuperscript{[25]} and the CVD risk factor reduction remained 10 years after the clinical trial.\textsuperscript{[26]}

IR correlated with CMR factors of WC, HbA1c, diastolic blood pressure and FPG. WC, which is a measure of abdominal obesity, is a modifiable CVD risk factor. Adipocytes in the abdominal region are now known to be metabolically active, producing such adipokines as leptin and resistin known to be associated with IR.\textsuperscript{[27]} Strategies to reduce WC, include increased physical activity, reduced alcohol consumption, and maintaining a healthy diet.\textsuperscript{[28]}

IR and hyperinsulinemia are prodromal states leading to poor glycemic control which underlie the metabolic dysregulations and cardiovascular complications of T2D.\textsuperscript{[13]} IR and the resulting hyperinsulinemia induce BP elevation by the activation of the sympathetic nervous system and renin-angiotensin-aldosterone system with consequential sodium retention and volume expansion, endothelial dysfunction, and alteration in renal function.\textsuperscript{[29]}

Multivariate regression analysis of IR on CMR factors identified FPG to be independently associated with IR showing that short-term glucose control is central to CVD risk reduction in the older Nigerians with T2D. The strength of the study lies in its relatively large sample size. Limitations of the study are its cross-sectional design that does not take into account longitudinal effects of risk factors of IR and prior treatment on study outcomes.

**Conclusion**

In elderly populations of Nigerians with T2D, IR as measured by FGIR correlated with CMR factors There was increased prevalence of CMR risk factors in older age groups with the highest duration of T2D. Poor short-term and long-term glucose control were higher in younger age groups showing a need to direct emphasis to this population of working age group. Polices in workplaces geared toward creating time for clinic visits may be useful. FGIR was independently associated with FPG, re-emphasizing focus on short-term blood glucose control in elderly diabetic populations. Future research on the effect of insulin sensitizers on CVD risk in this population may be useful.

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### Table 5: Multivariate regression of fasting glucose insulin ratio on cardio-metabolic risk factors of diastolic blood pressure, waist circumference, fasting plasma glucose and glycated haemoglobin in older adults with type 2 diabetes

| CMR factors            | Correlation coefficient | $P$  |
|------------------------|-------------------------|------|
| DBP                    | 0.254                   | 0.059|
| WC                     | -1.80                   | 0.187|
| FPG                    | 0.519                   | 0.003*|
| HbA1c                  | 0.143                   | 0.433|
| Duration of T2D        | 0.021                   | 0.874|
| Level of education     | 0.044                   | 0.734|

*Statistically significant. DBP - Diastolic blood pressure, FPG - Fasting plasma glucose, CMR - Cardio-metabolic risk, WC - Waist circumference, HbA1c - Glycated haemoglobin, T2D - Type 2 diabetes.
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Conflicts of interest

There are no conflicts of interest.

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