Original Article

Insulin Resistance and Hypertension among Type 2 Diabetes Subjects in a Tertiary Institution in South East Nigeria

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is frequently associated with hypertension (HTN), adding significantly to its overall morbidity and mortality. **Aim:** This study aimed to investigate the relationship between insulin resistance (IR) and blood pressure and other factors associated with both conditions. **Patients, Materials and Methods:** A case–control study of 180 subjects consisting of 60 with T2DM and HTN, 60 with T2DM and normal blood pressure, and 60 without T2DM or HTN (control). Sociodemographic, anthropometric, and clinical parameters were obtained from each subject and control. IR was derived from homeostasis model assessment (HOMA)-IR index calculated from fasting blood glucose and insulin. **Results:** The mean age of subjects with T2DM and HTN was 49.58 ± 10.50 years, that of subjects with T2DM and normotension was 48.50 ± 10.44 years, while that of controls was 48.85 ± 10.15 years. IR (HOMA-IR ≥2) was found in 96.7% of subjects with T2DM and HTN, 88.3% of those with T2DM and normotension, and 1.7% of subjects with neither of both conditions. Central obesity (Waist circumference "WC"), overweight, and obesity (BMI) significantly related to IR in subjects with T2DM and HTN (p = 0.020, 0.021 and 0.016 respectively) while only WC and obesity (BMI) significantly related to IR in subjects with T2DM and normotension (p = 0.001 and 0.036 respectively). **Conclusions:** There is a high prevalence of IR in T2DM subjects which is heightened by the presence of HTN.

Keywords: Hypertension, insulin resistance, type 2 diabetes mellitus

Introduction

Diabetes is one of the largest global public health concerns, imposing a heavy global burden on public health as well as socioeconomic development.[1] It is estimated that the total number of people with diabetes will rise from 171 million in 2000 to 366 million by 2030.[2] Hypertension (HTN) affects more than 55% of patients with diabetes and is about twice as common in persons with diabetes as in those without.[3] The prevalence of coexisting HTN and diabetes varies across different ethnic, racial, and social groups. Both diseases are independent risk factors for cardiovascular disease (CVD), and when they coexist, they multiply morbidity and mortality of CVD.[2,4] Insulin resistance (IR) and HTN are considered "diseases of civilisation" triggered by modern lifestyle, excessive food consumption, and sedentary lifestyle.[5] Diminished tissue sensitivity to insulin is characteristic of factors which include a large waist circumference (WC), HTN, hyperglycemia, dyslipidemia, and IR, all of which are commonly associated with increased risk of obesity and type 2 diabetes mellitus (T2DM).[5] Abundant clinical and epidemiologic evidence demonstrate a close linkage between IR and HTN.[5-7] The coexistence of IR and HTN results in a substantial increase in the risk of developing CVDs and T2DM.[5,6] HTN and DM are reportedly linked by IR as established in previous studies.[2,8] There are limited data on the possible role(s) of IR in the aetiology and sustenance of HTN among T2DM patients in Nigeria. A study done in Zaria, Nigeria, in 2009 found no statistically significant relationship between mean arterial blood pressure and homeostasis

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model assessment (HOMA)-IR in T2DM patients ($r = 0.087$, $P = 0.5350$).[9] A search of the literature did not show any study from the south-eastern part of the country. This study assessed the degree of IR in patients with DM and HTN compared to those with DM and normotension.

Patients, Materials and Methods

This was a case–control observational study conducted at the Endocrine and DM Clinic of the University of Nigeria Teaching Hospital, Enugu, between January and April 2019. T2DM subjects who consented to the study and satisfied the inclusion criteria were consecutively recruited. Ethical approval was obtained from the Ethics Committee of the hospital. Recruited subjects were labelled 'A' if they had DM and HTN, 'B' if they had DM with normal blood pressure, or 'C' if they had neither of the two conditions (control). The "C" group was recruited from the hospital community and patient relatives. They were assessed using modified semi-structured researcher-administered questionnaires. Anthropometric indices and blood pressure were obtained for each subject and control. The subjects were also examined for the skin manifestations of IR such as acanthosis nigricans, skin tags, hyperkeratosis, acne, frontal baldness, and hirsutism.

Fasting venous blood samples were obtained from each subject and control for the measurement of glucose and insulin. The sample was separated into two, one for glucose and the other for insulin assay. The sample for glucose was analysed within 24 h while that for insulin assay was centrifuged and the serum was refrigerated. The latter were analysed at the specialist chemical pathology laboratory within three months by enzyme-linked immunosorbent assay method using insulin assay kit from Immunospec Corporation Laboratories, USA. The kit had a specificity of 100%, a coefficient of variation of 5.5%, and a sensitivity of 2.0 μIU/ml (12 pmol/L). The batch number was 112100902.

IR was estimated with HOMA method as the product of fasting serum insulin (μU/mL) and fasting blood glucose (FBG) (mg/dl) divided by 405. A value of ≥2 was used in this study to define individuals with significant IR.[10] The sample size was calculated using the formula for calculating the minimal sample size for case–control study.[11] Inclusion criteria for the study subjects were T2DM patients aged between 30 and 70 years who were willing to participate in the study. Exclusion criteria included patients with a duration of DM >five years, subjects with type 1 DM (<30 years at the time of diagnosis and required insulin for survival), nondiabetic patients, pregnancy, patients on insulin or who had DM nephropathy, presence of acute complications of DM, and subjects that had significant alcohol intake or used tobacco in any form.

Statistical analysis

Data obtained from each patient and control subject were entered and analysed using the Statistical Package for Social Sciences software for Windows (version 20.0). Descriptive analysis was carried out on categorical and continuous variables using frequency, percentages, means, and standard deviations. Means of continuous variables were compared using analysis of variance and Kruskal–Wallis test where appropriate. Associations between categorical variables were determined using Chi-square, Fisher's exact test, or logistic regression where appropriate. $P < 0.05$ was considered statistically significant. Results are presented in Tables and Charts.

Results

Table 1 shows the equal distribution of age and gender of the studied subjects. However, subjects with T2DM and HTN had statistically significant systolic blood pressure, diastolic blood pressure, WT, body mass index (BMI), and WC compared to those with only T2DM and the control group. There was, however, no significant difference in the waist-to-hip ratio (WHR) between subjects with T2DM and HTN, subjects T2DM only, and normal subjects.

Table 2 shows that subjects with T2DM and HTN had statistically significantly higher blood glucose, FSI, and IR than those with only T2DM and controls ($P < 0.001$, $F = 47.345$).

Table 3 shows that subjects with T2DM and HTN were 1711 times more likely to have IR than the control subjects, while subjects with T2DM only were 446 times more likely to have IR than normal control subjects.

Table 4 shows that among the subjects with T2DM and HTN, there was no statistically significant difference in IR between age category, gender, duration of DM, abnormal WHR, and duration of HTN among the studied subjects. However, obese subjects were 98 times more likely to have IR than normal subjects, overweight subjects were 32 times more likely to have IR than controls, while subjects with abnormal WC were 57 times more likely to have IR than normal subjects.

Table 5 shows that in subjects with only T2DM, obesity and abnormal WC were associated with significant IR than in normal subjects, while abnormal WHR, overweight and FSI category did not have significant association with IR in normal subjects.

Discussion

The prevalence of IR among subjects with DM and HTN in this study was 92.5%, that for subjects with only HTN was 88.3%, while that of control subjects was 1.7% [Figure 1]. The result adds to other studies done on IR in diabetic subjects around the world. In an earlier study in Enugu by Oli *et al*., the prevalence of IR among DM subjects was 95.2% while that of control subjects was 75.8%.[10] This wide discrepancy in the prevalence of IR in the control group could have been because the earlier study had a smaller number of control subjects (33), and did not exclude control subjects who used tobacco or had significant alcohol intake. Another reason could have been that control subjects who had HTN or a first degree relative with HTN were also not excluded like we did in this study.

Table 1: Clinical characteristics of the study population (expressed as mean±standard deviation)

Sex	T2DM and HTN, *n* (%)	T2DM only, *n* (%)	Control, *n* (%)	χ^2	*P*
Male	22 (36.7)	23 (28.3)	29 (48.3)	1.973	0.373
Female	38 (63.3)	37 (61.7)	31 (51.7)		
	T2DM and HTN	**T2DM only**	**Control**	***F***	***P***
Age	49.58±10.50	48.50±10.44	48.85±10.15	0.171	0.843
SBP	136.00±12.78	116.83±9.99	116.50±9.36	63.925	<0.001*
DBP	85.17±9.65	75.17±5.37	74.17±6.19	41.559	<0.001*
WT	75.63±12.03	69.85±11.90	74.12±7.08	`4.812	0.009*
BMI	28.26±4.16	24.89±4.93	25.72±2.27	11.879	<0.001*
WC (male)	94.91±13.55	88.39±9.65	91.21±4.19	6.666	0.007*
WC (female)	96.24±10.16	86.43±8.55	88.09±5.27	14.432	<0.001*
WHR (male)	0.97±0.07	0.98±0.06	0.99±0.03	2.433	0.095
WHR (female)	0.94±0.07	0.94±0.04	0.96±0.02	2.298	0.106

T2DM: Type 2 diabetes mellitus, HTN: Hypertension, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index, WC: Waist circumference, WHR: Waist-to-hip ratio, WT: Weight

Table 2: Blood glucose and insulin resistance of the subjects and controls (expressed as mean±standard deviation)

	T2DM and HTN	T2DM only	Control	*F*	*P*
FBG	186.60±73.59	169.08±45.28	102.27±7.97	47.345	<0.001
FSI	16.85 (138.36)*	7.10 (99.91)*	2.40 (33.23)*	NA	<0.001
IR	7.40 (138.27)*	3.11 (101.59)*	0.56 (31.64)*	NA	<0.001

*Median (mean rank) for a Kruskal–Wallis test. IR: Insulin resistance, T2DM: Type 2 diabetes mellitus, HTN: Hypertension, FBG: Fasting blood glucose, FSI: Fasting serum insulin, NA: Not available

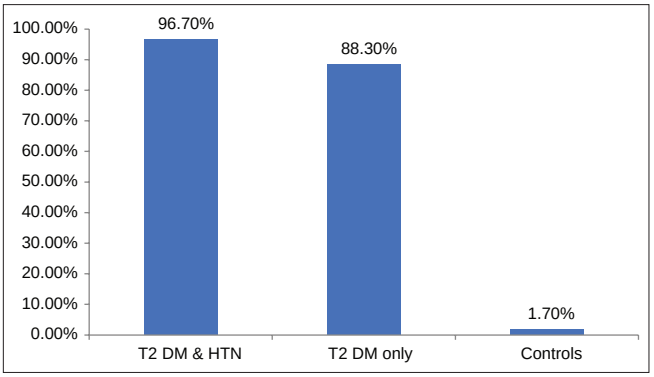

Figure 1: Prevalence of insulin resistance among subjects with diabetes mellitus and hypertension, subjects with diabetes mellitus only, and those with neither of the two

Previous studies have shown that HTN, smoking, alcohol misuse, and being a first degree relative of a T2DM patient are all positively associated with IR.[12-14] The prevalence of IR was found to be 87.5% and 27.8% among DM patients and controls, respectively, by Bakari and Onyemelukwe in Northern Nigeria.[15] The discrepancies may be because they had a smaller sample size of subjects and controls, selected only subjects with "good" and "acceptable" blood glucose control, and did not exclude individuals with HTN. Among adults in the USA, similar rates of IR between African Americans and white Americans with T2DM, and a dichotomous population of African Americans with T2DM with 50% exhibiting IR, have been reported.[16] A prevalence of 85.1% was found among Pakistani diaspora.[17] The prevalence was found to be 86% in Indians.[18] In Ghana, the IR assessed by HOMA was four times greater in T2DM patients than in those with normal blood glucose.[19] A significant finding in the subjects studied was the presence of high blood glucose levels. This was similar to the finding in an earlier study at this centre which found the mean FBG to be 185 ± 97.2.[20] Another multicentre study in Nigeria found the mean fasting plasma glucose of 187 ± 4.6.[21] This could predispose to glucotoxicity and heightened IR in T2DM patients.[10,22]

This study showed that IR is more prevalent in T2DM subjects with HTN than those without (96.7% vs. 88.3%). This suggests that the presence of HTN in patients with T2DM increases their likelihood of having IR. Hyperinsulinemia, which is considered a surrogate marker of IR, was found in 50% of hypertensive nondiabetic subjects.[5,23] In another study, the prevalence of insulin resistance was 30% in subjects with hypertension, 9.6% in those with prehypertension, and 0.9% in subjects with normal blood pressure.[24] In Nigeria, Akande *et al*.[25] found that IR was present in 31.4% of hypertensive subjects and 8.6% of controls.[13] In untreated essential hypertensive patients, fasting and postprandial insulin levels were higher than normotensive controls, regardless of the BMI, and there was a direct correlation between plasma insulin concentrations and blood pressure.[13,26] Since HTN in an insulin-resistant state independent of obesity and blood glucose[27] and IR is found in most studies to be more than 90% in T2DM patients in Nigeria,[10,28] it then follows that T2DM subjects with HTN should have more degree of IR, as shown in this study. More studies need to be done to determine whether IR precedes or is an outcome of HTN.

In this study, obesity, overweight, and abnormal WC were found to be significantly associated with IR in subjects with T2DM and HTN, while only obesity and abnormal WC were significantly associated with IR in subjects with T2DM and normotension. In other studies, done in Nigeria, Raimi found

Table 3: Insulin resistance in type 2 diabetes mellitus subjects with hypertension and normotension

	IR		*P*	OR	95% CI for OR
	Yes, *n* (%)	No, *n* (%)			
T2DM and HTN	58 (96.7)	2 (3.3)	<0.001	1711.00	150.984–19389.609
T2DM only	53 (88.3)	7 (11.7)	<0.001	446.714	53.200–3751.041
Controls	1 (1.7)	59 (98.3)			

T2DM: Type 2 diabetes mellitus, HTN: Hypertension, IR: Insulin resistance, OR: Odds ratio, CI: Confidence interval

Table 4: Association between insulin resistance and other factors in subjects with type 2 diabetes and hypertension

	IR		*P*	OR	95% CI for OR
	Yes, *n* (%)	No, *n* (%)			
Age					
<44	24 (100.0)	0 (0.0)	0.998	95027	0.000–NA
45 and above	34 (94.4)	2 (5.6)			
Sex					
Male	21 (95.5)	1 (4.5)	0.694	0.568	0.034–9.551
Female	37 (97.4)	1 (2.6)			
Duration of diabetes (months)					
≤12	20 (95.2)	1 (4.8)	0.656	0.526	0.031–8.867
>12	38 (97.4)	1 (2.6)			
Duration of hypertension (months)					
≤12	19 (95.0)	1 (5.0)	0.618	0.487	0.029–8.219
>12	39 (97.5)	1 (2.5)			
BMI					
Obese	31 (100.0)	0 (0.0)	0.016	98.000	1.521–1911.104
Overweight	26 (96.3)	1 (3.7)	0.021	32.000	2.999–223.111
Normal	1 (50.0)	1 (50.0)			
WC category					
Abnormal	57 (98.3)	1 (1.7)	0.020	57.000	1.893–1715.947
Normal	1 (50.0)	1 (50.0)			
WHR category					
Abnormal	54 (98.2)	1 (1.8)	0.084	13.500	0.705–258.452
Normal	4 (80.0)	1 (20.0)			

IR: Insulin resistance, OR: Odds ratio, CI: Confidence interval, BMI: Body mass index, WC: Waist circumference, WHR: Waist-to-hip ratio, NA: Not available

that the correlation between IR and the anthropometric indices was best with WC, and least with WHR, and that of the three indices of obesity, WC contributed most to HOMA-IR.[29] Akande *et al*. found that BMI was the only anthropometric index that significantly predicted IR[13] while Oli *et al*. found that BMI and WC (but not WHR) significantly predicted IR.[10] This is similar to what was found in this study in both hypertensive and normotensive diabetic subjects. The excessive intake of food, sedentary lifestyle, westernisation, and lack of physical activity are responsible for the growing epidemic of obesity and the increasing prevalence of T2DM in many parts of the developing world, including Nigeria.[30]

Being overweight also significantly predicted IR in T2DM subjects with HTN but not those with normotension in this study. This could be because those with T2DM and HTN had an added feature of the metabolic syndrome (HTN) and therefore a higher degree of IR than those with normotension. Overweight and obese subjects even without IR are at a higher risk of developing HTN and blood pressure progression.[31] Being obese also predisposes to a rise in blood pressure.[32]

The pathophysiological linkages between DM, HTN, and IR include factors such as sedentary lifestyle, excessive caloric intake, and increased adiposity. Sedentary lifestyle and excessive caloric intake can lead to increased adiposity which has been associated with increased risk of worsening IR. IR has been linked in turn to an increased vascular oxidative stress, inflammation, and endothelial dysfunction characterised by diminished vascular nitric oxide bioactivity, all of which promote vascular stiffness resulting in a persistent elevation of blood pressure and the promotion of CVD.[33] Moreover, hyperinsulinemia which is found in subjects with T2DM and IR, leads to sodium retention, increased intracellular volume, and HTN.[34] Furthermore, premature vascular aging, autonomic nervous system dysregulation, inappropriate activation of the renin–angiotensin–aldosterone system, and the sympathetic nervous system contribute to the pathogenesis of obesity, IR, T2DM, and HTN.[35]

Table 5: Association between insulin resistance and other factors in subjects with type 2 diabetes only

	IR		*P*	OR	95% CI for OR
	Yes, *n* (%)	No, *n* (%)			
Age					
<44	20 (80.0)	5 (20.0)	0.109	0.242	0.043–1.369
45 and above	33 (94.3)	2 (5.7)			
Sex					
Male	19 (82.6)	4 (17.4)	0.286	0.419	0.085–2.073
Female	34 (91.9)	3 (8.1)			
Duration of diabetes (months)					
≤12	25 (89.3)	3 (10.7)	0.830	1.190	0.242–5.844
>12	28 (87.5)	4 (12.5)			
BMI					
Obese	27 (96.4)	1 (3.6)	0.036	25.800	2.785–238.988
Overweight	17 (89.5)	2 (10.5)	0.668	1.466	0.256–8.397
Normal	9 (69.2)	4 (30.8)			
WC category					
Abnormal	43 (97.7)	1 (2.3)	0.001	25.800	2.785–238.988
Normal	10 (62.5)	6 (37.5)			
WHR category					
Abnormal	50 (89.3)	6 (10.7)	0.407	2.778	0.248–31.126
Normal	3 (75.0)	1 (25.0)			
FSI category					
Abnormal	52 (89.7)	6 (10.3)	0.144	8.667	0.478–157.157
Normal	1 (50.0)	1 (50.0)			

IR: Insulin resistance, OR: Odds ratio, CI: Confidence interval, BMI: Body mass index, WC: Waist circumference, WHR: Waist-to-hip ratio, FSI: Fasting serum insulin

There was no significant association between the age of the subjects and IR in this study, although IR is known to increase with age.[36] This could be because approximately 90% of the subjects studied were in the young and middle age bracket. However, age has been shown not to have an independent effect on insulin sensitivity as reductions in insulin sensitivity associated with aging are likely due to age-related increase in adiposity and/or decreased physical activity rather than a consequence of advanced chronological age.[37] Hence, more studies need to be done to further elucidate the cause of age-related increase in IR.

There was also no significant association between the duration of T2DM and IR. Some studies found a negative correlation between the degree of IR and the duration of T2DM,[38,39] while others found a positive correlation.[40,41] In this centre, Oli *et al*. found that the duration of T2DM positively correlated with and predicted IR[10] This discrepancy with the finding in this study could have been because, in the earlier study, the subjects were not limited to those that were recently diagnosed with T2DM. With long-standing T2DM in subjects with poor glycemic control and the attendant glucotoxicity, the degree of IR is bound to be higher.

Conclusions

1. There is a high prevalence of IR in T2DM patients at the UNTH diabetes clinic
2. The degree of IR is higher in subjects with T2DM and HTN than in subjects with only T2DM
3. Most subjects without T2DM and HTN do not have significant IR
4. Although most T2DM patients had IR, they did not have the skin manifestations of IR. This shows that those features cannot be relied upon as a pointer to the presence or otherwise of IR in T2DM subjects in this centre.

Recommendations

Measurement of anthropometric indices, especially WC and BMI, should continue to be used as a screening tool to identify individuals with IR in T2DM setting. This is in view of the fact that abnormalities in these parameters add to the already existing CVD burden in them. Overweight individuals should be screened for other conditions associated with IR such as T2DM, HTN, and dyslipidemia. This will ensure early diagnosis, management, and better cardiovascular outcome.

Limitations of the study

1. HOMA-IR index used for this study is only a surrogate measure of IR
2. HBA1c, which is a better indicator of glycemic control, was not assessed due to financial constraints.

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Conflicts of interest

There are no conflicts of interest.

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