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Research Article

Association of Peripheral Artery Disease, Peripheral Neuropathy and Insulin Resistance among Patients with Type 2 Diabetes mellitus in Ekiti, Nigeria

***Raimi T.H. [1], Akintoye O.O.[2], Ajayi D.D.[3], Ibidapo O. R.[4]**

[1]*Department of Medicine, Ekiti State University/ Ekiti State University Teaching Hospital, Ado-Ekiti*
[2]*Department of Physiology, Ekiti State University, Ado-Ekiti*
[3]*Department of Chemical Pathology, Ekiti State University Teaching Hospital*
[4]*Department of Medicine, Ekiti State University Teaching Hospital*

ABSTRACT

Peripheral Arterial Disease (PAD), a reflection of systemic atherosclerosis, is a clinical condition that manifests as atherosclerosis of the lower limb. The study determined the association among PAD, peripheral neuropathy (PN), and insulin resistance (IR) in patients with type 2 diabetes mellitus (T2DM). A cross-sectional study was conducted among patients with T2DM attending the endocrine clinic of Ekiti State University Teaching Hospital (EKSUTH), Ado-Ekiti, between October to December 2018. Demographic information such as age, gender, and duration of diabetes were documented in a questionnaire, while anthropometry, systolic and diastolic blood pressures (SBP & DBP) were determined. PAD, PN, and IR were determined by Ankle Brachial Index (ABI), vibration perception threshold (VPT) to biothesiometer and homeostasis model (HOMA2-IR) respectively. Association among variables of interest was determined with Pearson's Chi-Square, Student's t test, and Pearson's correlation. There were 90 participants, with a mean age of 58.7(11.6) years. The prevalence of PAD was 40% (37.0% in men and 40.7% in women, p =0.36), and 12.2% had moderate PAD. Compared to patients without PAD, those with PAD had higher mean HOMA2-IR (3.71 vs 2.01, p<0.001), glycosylated haemoglobin (HbAic) (9.4% vs 7.7%, p=0.004), and SBP (135.6mmHg vs 126.9mmHg, p=0.025), and more likely to have PN (67.7% vs 26.7%, p<0.001. ABI negatively correlated with HOMA2-IR (r=-0.403, p<0.001), HbAic (r= -0.347, p=0.001), SBP (r=-0. 391, p<0.001), DBP (r=-0.22, p=0.037), and duration of diabetes (r=-0.251, p=0.042). Peripheral arterial disease (PAD) was more prevalent among T2DM patients with neuropathy.Insulin resistance positively correlated with vibration perception threshold. All diabetic patients with PN should be screened for PAD.

Keywords: *Peripheral arterial disease, peripheral neuropathy, insulin resistance, type 2 diabetes*

*Author for correspondence: Email: taiwo.raimi@eksu.edu.ng; *Tel: +234 802 7762 647*

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INTRODUCTION

Peripheral arterial disease (PAD) is a clinical condition that manifest as atherosclerosis of the lower limb. Since PAD is a reflection of systemic atherosclerosis, it is associated with renovascular, coronary artery, and cerebrovascular diseases, with the attendant increased morbidity and mortality (Hajibandeh *et al*., 2017). It was estimated that PAD affects over 236 million people worldwide in 2015, and is particularly frequent in diabetic patients with worse outcomes, such as lower extremity amputation and cardiovascular disease (Thiruvoipati *et al*., 2015) (Song *et al*., 2019).

Thus, early diagnosis or identification and treatment of PAD in patients with T2DM is important or will go a long way in preventing the associated morbidity and mortality. Unfortunately, PAD is often asymptomatic among persons with diabetes, and the presence of peripheral neuropathy may contribute to this undesirable phenomenon (Oyelade *et al*., 2012). The prevalence and severity of PAD have been documented to be greater in diabetic peripheral neuropathy (Nichols, 2014), and current thinking suggests a convergence in the pathogenesis of the two diabetic complications. Additionally, it has been suggested that neuropathy predates PAD in patients with T2DM. Universal screening for PAD among people with DM is still controversial

Insulin resistance is a major pathophysiological defect in T2DM, and it has been associated with PAD (Britton *et al*., 2012). Ethnic differences in the prevalence of PAD occurs (Kullo *et al*., 2003) (Vitalis *et al*., 2017), and genetic predisposition is being suspected (Nativel *et al*., 2018). PAD is more prevalent in blacks than white, and the former is more insulin resistant for a given adiposity than the latter (Vitalis *et al*., 2017) (Guerrero *et al*., 2009). Clearly, IR can be genetically determined (Brown and Walker, 2016). Previous studies on PAD in Nigeria did not explore its relationship with IR (Ogbera *et al*., 2015) (Soyoye *et al*., 2016).

Can the presence of neuropathy identify patients with DM who should be screened for PAD? Is there a correlation between IR and PAD among Nigerians with T2DM? The present study aims to answer these questions. We hypothesize that PAD will be more prevalent among T2DM patients with neuropathy. We also hypothesize that HOMA-IR, a measure of insulin resistance will correlate with ABI and vibration perception threshold. Since cost and availability may preclude universal screening, knowledge gained from this study can make room for a more efficient screening and management of PAD in patients with T2DM.

MATERIALS AND METHODS

Study design and Participants: A cross-sectional study was conducted among patients with T2DM attending the endocrine clinic of Ekiti State University Teaching Hospital (EKSUTH). Consecutive patients with T2DM who have attended the clinic for at least 6 months were conveniently recruited between October to December 2018 (both months inclusive). These were either being managed with oral antidiabetics and/or insulin.

Ethical consideration: Written informed consent was obtained from each participant and approval was given by the Ethic and research committee of EKSUTH (EKSUTH/A67/2016/12/005)

Procedure and measurements: Demographic information such as age, gender, duration of diabetes, alcohol intake and smoking were documented in a questionnaire, while clinical and laboratory measures of interest were determined by standard protocols. The height was measured (in meters) to the nearest 0.1metre with a stadiometer with the participants barefooted. The weight was measured (in kilograms) with a weighing scale without shoes and with the patient wearing light clothing, to the nearest 0.1kg. Body mass index was calculated from the values of weight (kg) and height (m) as weight/(height)^2. Waist circumference (in centimeters) was measured at the level of the umbilicus with a non-stretchable tape rule. Waist-to height ratio was calculated as waist circumference (centimeters) divided by height (centimeters).

The peripheral arterial disease was defined as a reduction in ankle brachial index determined with handheld vascular doppler, (L150R Diabetic Foot Care India PvT Ltd.) with a 8MHz probe. For ABI determination, the systolic blood pressure (SBP) in mmHg, of the two brachial arteries, posterior tibial and dorsalis pedis arteries were measured in the supine position and documented. The ratio of the higher brachial to higher ankle SBP was calculated for both limbs, and the lower ABI value chosen for an individual. PAD was defined as ABI<0.9 and further categorized as mild (ABI, 0.80-0.89), moderate (ABI, 0.50-0.79) and severe (ABI, <0.50) (Vowden & Vowden, 2001). We determined DM neuropathy with a vibration perception threshold (VPT) to a portable digital biothesiometer (Diabetic Foot Care, India PVT Limited, Tamil Nadu, India). The device has a vibration output range of 0-50 volts operating at a frequency of 120Hz. The vibrating probe was applied to 5 points (hallux, under 1st, 3rd and 5th metatarsals, and heel) on the plantar surface of the foot, and the voltage increased slowly until the subject perceived the vibration. The average of the five values was recorded for each foot and the higher threshold of the two limbs was taken as the VPT for the subject. We defined DM neuropathy as vibration perception threshold >16 mV irrespective of neuropathic symptoms (Young *et al*., 1994).

Laboratory analysis: For determination of HOMA-IR, fasting insulin and plasma glucose were determined on venous blood samples obtained by aseptic techniques, after an overnight fast. Fasting insulin concentration was measured with an immunoradiometric assay (INS-IRMA; Biosource, Nivelles, Belgium) while the glucose oxidase method was used to measure plasma glucose. HOMA2-IR was calculated using a software implementation of the HOMA2 model, (Oxford University HOMA2 calculator V2.2.3) (https://www.dtu.ox.ac.uk/homacalculator/). HbAic assay was done immediately on capillary blood using a fully automated boronate affinity method (Clover HbAic analyzer - INFOPIA Co., Ltd, Korea.)

Data analysis: Continuous data was presented as means (sd) and compared with student's t test while categorical data was presented as percentages and compared with Chi-square. Pearson's correlation was employed to determine the association between ABI with clinical, anthropometry and laboratory variables. Relationship between PAD and peripheral neuropathy was determined by Chi-square. Analysis was performed with Statistical Package for Social Sciences (IBM SPSS) version 25 for Windows (IBM Corp., Armonk, N.Y., USA), and level of statistical significance was set at $p<0.05$

RESULTS

There were 90 participants, with a mean age of 58.7(11.6) years. Out of these, 86 (comprising 59 women or 68.6%) had complete data. The prevalence of PAD was 40% (37.0% in men and 40.7% in women, p =0.36), and 12.2% had moderate PAD. Except for indices of general and central obesity, and LDL, there were no differences in the mean of clinical and laboratory parameters between men and women (Table 1).

Compared to patients without PAD, those with PAD had higher mean HOMA2-IR (3.71 vs 2.01, p<0.001), HbAic (9.4% vs 7.7%, p=0.004), and SBP (135.6mmHg vs 126.9mmHg, p=0.025), and more likely to have neuropathy (67.7% vs 26.7%, p<0.001) [Table 2 & Fig. 1]. Table 3 shows the correlation between ABI with clinical and laboratory parameters in all participants. ABI negatively correlated with HOMA-IR (r=-0.403, p<0.001), HbAic (r= -0.347, p=0.001), SBP(r=-0. 391, p<0.001), DBP (r=-0.22, p=0.037), and duration of diabetes (r=-0.251, p=0.042). No significant correlation between ABI and other parameters. Correlation was not done separately for each gender because they had similar mean for most of the parameters.

Table 1:

Clinical and laboratory characteristics of the participants

Characteristics	Both sexes N=86	Male N=59	Female N=27	P
Age	58.69 (11.55)	58.89 (12.27)	58.76 (11.55)	0.963
DM duration	5.67 (4.67)	5.38 (5.15)	5.78(4.52)	0.755
BMI	28.07 (4.7)	26.00 (3.77)	29.237(4.74)	0.002
WC	94.36 (10.81)	87.17 (8.72)	97.16(10.26)	0.000
WHtR	.59 (0.07)	0.53 (0.06)	0.61(0.07)	0.000
SBP	130.38 (18.34)	127.15 (19.45)	130.78(17.87)	0.397
DBP	82.17 (10.81)	81.41(10.84)	82.02 (11.04)	0.812
HbAic	8.4 (2.8)	8.2 (3.1)	8.2(2.6)	0.925
Triglyceride	1.15 (0.97)	1.06 (0.59)	1.21(1.12)	0.494
TC	5.50 (1.97)	4.99 (1.61)	5.78(2.13)	0.090
LDL-C	4.02 (1.88)	3.46 (1.44)	4.33(2.03)	0.046
HDL-C	1.15 (0.35)	1.07 (0.35)	1.19(0.35)	0.153
HOMA-IR	2.69 (2.09)	2.98 (2.05)	2.65(2.14)	0.510
VPT	24.61(14.75)	26.65 (17.26)	23.84(13.76)	0.508
ABI	0.91(0.13)	0.92 (0.14)	.91(0.12)	0.602
PAD (%)	40.0	37.0	40.7	0.360
Mild PAD (%)	27.8	18.5	30.5	
Moderate PAD (%)	12.2	18.5	10.2	

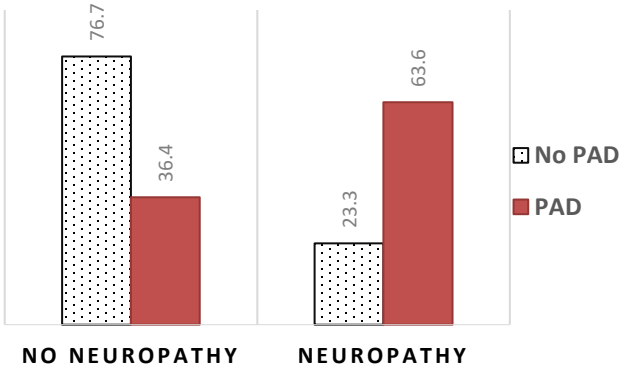
BMI, body mass index; WC, waist circumference; WHtR, waist-to height ratio; HbAic, glycosylated haemoglobin; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; HOMA-IR, homeostasis model for insulin resistance; VPT, vibration perception threshold; ABI, ankle brachial index; PAD, peripheral arterial disease SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus

Table 2:
Characteristics of patients with or without PAD

Characteristics	No PAD n=43	PAD n=33	P
Age (years)	57.23 (11.1)	60.8 (12.1)	0.149
DM duration(years)	5.30 (4.7)	6.08 (4.7)	0.503
BMI (kgm^2)	28.09(4.7)	28.0 (4.8)	0.944
WC(cm)	94.4 (10.4)	94.3 (11.6)	0.940
WHtR	0.59 (0.07)	59 (0.08)	0.865
SBP(mmHg)	126.9 (17.7)	135.6 (18.2)	0.025
DBP(mmHg)	80.83 (9.88)	84.2 (11.9)	0.163
VPT (volts)	17.99 (10.29)	33.3 (15.3)	0.000
HbAic	7.7 (2.3)	9.4 (2.6)	0.004
HOMA2-IR	2.01(1.6)	3.7(2.3)	0.000

Legends: BMI, body mass index; WC, waist circumference; WHtR, waist-to height ratio; HbAic, glycosylated haemoglobin; HOMA-IR, homeostasis model for insulin resistance; VPT, vibration perception threshold; PAD, peripheral arterial disease SBP, systolic blood pressure; DBP, diastolic

Figure 1:
Prevalence of PAD in relation to neuropathy
PAD = peripheral arterial disease



X^2= 12.6. p<0.001.

Table 3:

Correlation between ABI with clinical and laboratory parameters in all participants

Variable	R	p
Age	0.131	0.221
Duration of DM	-0.251	0.042
BMI	0.029	0.786
WC	0.034	0.754
WHtR	0.015	0.889
SBP	-0.391	0.010
DBP	-0.220	0.037
VPT	-0.505	<0.001
HbAic	-0.347	0.001
TG	0.161	0.131
TC	-0.125	0.240
LDL-C	-0.081	0.449
HOMA2-IR	-0.403	<0.001

BMI, body mass index; WC, waist circumference; WHtR, waist-to height ratio; HbAic, glycosylated haemoglobin; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HOMA-IR, homeostasis model for insulin resistance; VPT, vibration perception threshold; SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus.

DISCUSSION

Peripheral arterial disease (PAD) is a devastating complication of T2DM, and its early diagnosis helps to identify patients at risk of limb loss, disability, stroke, myocardial infarction and death (2003). Since PAD may be asymptomatic in patients with T2DM, and these asymptomatic patients tend to have worse disease and outcome (Hajibandeh *et al*., 2017), one method of achieving its early diagnosis is universal screening of all patients with T2DM, through ABI determination. Indeed, this method have been recommended by some authors (Weragoda *et al*., 2016). But this may not be cost effective and/or practicable in resource poor settings like ours. Another method is identifying high risk patients, thus enabling efficient screening for, and treatment of PAD. Insulin sensitizers will correct

hyperglycaemia, while at the same time improve the vascular anomalies resulting in PAD (Althouse *et al*., 2013). Thus, identifying PAD early may influence the choice of antidiabetics (Buso *et al*., 2019). In this context, this study elucidated or determined the association of PAD, PN and IR among patients with T2DM. We also determined the correlates of ABI among the participants.

We found that the prevalence of PAD was 39.5%, and none of the participants had severe PAD. We also found that ABI negatively correlated with VPT and IR. Other negative correlates of ABI include duration of diabetes, SBP, DBP, and HbAic. Similarly, the mean of VPT, HOMA-IR, HbAic and SBP were higher among patients with PAD. Furthermore, PAD was significantly more prevalent among patients with peripheral neuropathy. We did not find significant correlation between ABI and anthropometric and lipid parameters. Since very few patients (4.3%) gave history of past smoking, and none with current smoking, we did not determine any association of PAD with smoking. Besides, they all had normal ABI.

The prevalence of PAD in this study was similar to the reported values of 40% by Ogbera *et al* (Ogbera *et al*., 2015) but higher than 22% reported by other Nigerian authors (Soyoye *et al*., 2016). The lower prevalence in the latter study may be due to exclusion of patients with foot ulcers. Significant number of patients with foot ulcer do have PAD (Mejias and Ramphul, 2018). Additionally, their study participants had lower mean HbAic in comparison to ours. HbAic has been reported to be associated with arterial stiffness (Lee *et al*., 2016), and we found that it correlated with ABI in this study. In the study by Oyelade *et al*., (Oyelade *et al*., 2012) PAD was present in 52.5% of diabetic patients. The higher prevalence may be attributable to restriction of their study participants to middle-age and the elderly (50-89 years).

In contrast to our findings, 12.5% of patients with diabetes had moderate to severe PAD in a report by Okello *et al*. (Okello *et al*., 2014). But many of their participants were former/current smokers unlike our cohort. Smoking is a major risk factor for PAD. Several authors have reported significant positive association between smoking and low ABI/PAD (Adler *et al*., 2002) (Li *et al*., 2012, Yokoyama *et al*., 2014) (Weragoda *et al*., 2016, Mejias and Ramphul, 2018). Recent systematic review and meta-analysis confirm the role smoking in PAD, the effect that was found to be greater than that of coronary artery disease(Lu *et al*., 2014) (Song *et al*., 2019). However, a study did not find any association between smoking and PAD, most likely due to the few number (32 out of 600 or 5.3%) of active smokers in that study (Mejias and Ramphul, 2018). Smoking causes endothelial dysfunction, and induces inflammatory response, a major pathogenic disorder in PAD (Ambrose and Barua, 2004). Additionally, smoking adversely influences the oxidation of LDL.

We found a negative correlation between ABI and blood pressure, and participants with PAD had higher SBP. Hypertension is an established cause of PAD, and has been reported to be associated with PAD in cross-sectional and prospective studies, as well as systematic reviews (Hua *et al*., 2016, Weragoda *et al*., 2016) (Mejias and Ramphul, 2018) (Song *et al*., 2019) (Mufti Alsadiqi *et al*., 2019). The shear stress due to high blood pressure causes endothelial dysfunction, in addition to abnormal rheology, and altered blood constituents (Makin *et al*., 2001). These abnormalities contribute to plaque formation and atherosclerosis.

There is convergence in the pathogenesis of PAD and PN. Traditionally, PAD and PN are viewed as macrovascular and microvascular diseases respectively. But current thinking implicates microvascular disorder in the development of macrovascular disease (Fiordaliso *et al*., 2016). Therefore, it is not surprising that ABI correlated with VPT in our study, coupled with the finding that PN was more prevalent among those with PAD. Several authors have also reported association between PAD and PN (Li *et al*., 2012) (Nichols, 2014, Mejias and Ramphul, 2018). In the study by Ogbera *et al*., (Ogbera *et al*., 2015) more than 50% of the patients with PN also had PAD . Among patients withT2DM, it was reported that more than four-fifth (>80%) of limbs in those with PAD had evidence of PN (Kim *et al*., 2014). In a study by Nichol (Nichols, 2014), presence of peripheral neuropathy increased the probability of having PAD by more than two-fold.

ABI negatively correlated with HbA1c in our study, suggesting that those with poor long-term glucose control were more likely to have PAD. This is consistent with previous reports (Velescu *et al*., 2016). Specifically, Velescu *et al*., reported that poorly controlled diabetes predicted PAD by about 10-fold (Velescu *et al*., 2016). Previous studies in Nigeria also demonstrated that level of glycaemic control predicted PAD (Ogbera *et al*., 2015). Glycated haemoglobin has been associated with atherosclerosis even before the onset of diabetes (Lee *et al*., 2016). In the landmark UKPDS study, 28% increased risk of PAD was associated with each 1% rise in HbA1c (Adler *et al*., 2002). Glycation of proteins promotes endothelial dysfunction, resulting in inflammation and impaired generation of nitric oxide, and ultimately leucocyte dysfunction and plaque formation (Thiruvoipati *et al*., 2015). Furthermore, we found that ABI correlated with duration of diabetes. This agrees with previous reports (Umuerri and Obasohan, 2013) (Weragoda *et al*., 2016) (Shukla *et al*., 2018) and is not unexpected given the progressive nature of T2DM.

Measure of insulin resistance negatively correlated with ABI in our study, and mean of HOMA2-IR was greater among those with PAD. Additionally, HOMA2-IR positively correlated with VPT (right limb, r=0.348, p, 0.002; left limb, r=0.275, p, 0.016). Some workers also reported that both ABI and PAD demonstrated associations with insulin resistance (Britton *et al*., 2012). In their study, compared with the first quartile, the fourth quartile of HOMA-IR was associated with greater risk for PAD (Britton *et al*., 2012). In another study insulin resistance was found be strongly and independently associated with PAD (Pande *et al*., 2008). The above study also suggested that the causal role of inflammation in the genesis of PAD is dependent on insulin resistance. IR contributes to chronic hyperglycaemia in T2DM. These two conditions result in generation of reactive oxygen species, oxidative stress and inflammation, and ultimately microvascular and macrovascular disease (Paneni *et al*., 2013) (Nativel *et al*., 2018). Thus, insulin resistance can result in both PAD and PN. This may explain the frequent coexistence of microvascular (e.g PN) and macrovascular (e.g PAD) complications in patients with T2DM.

Theoretically, insulin sensitizers should prevent or retard the progression of PAD and PN. Indeed, some workers have demonstrated the beneficial effect of insulin sensitizers in the prevention of PAD and its outcomes (Althouse *et al*., 2013). Furthermore, metformin has been demonstrated to be associated with a reduction in vascular calcification, thus making it a choice for high-risk individuals (Mary *et al*., 2017).

The present study confirmed our hypotheses, namely that PAD will be more prevalent among T2DM patients with neuropathy; and that HOMA-IR will correlate with ABI and vibration perception threshold. However, the study is limited by the sample size. Thus, a larger study is necessary to further confirm our findings. The effects of medications such as statins, metformin etc. on the outcome measures were not studied. These may attenuate some of our findings.

In conclusion, peripheral arterial disease (PAD) was more prevalent among T2DM patients with neuropathy. Ankle brachial index (ABI) negatively correlated with duration of diabetes, systolic blood pressure, glycosylated hemoglobin, and vibration perception threshold (VPT), while insulin resistance positively correlated with vibration perception threshold (VPT). Considering, the morbidity and mortality associated with PAD, its frequent coexistence of PN may imply that all patients with PN should be screened for it.

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