Skin Manifestations of Peripheral Artery Disease: Prevalence and Diagnostic Utility

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Abstract

Introduction: Peripheral artery disease (PAD) is a common but underdiagnosed arm of the cardiovascular triad. Reliance on the presence of skin manifestations of chronic lower limb ischemia may result in clinical inertia in the diagnosis of PAD. Objective: Literature on the skin manifestations of PAD is limited. This paper aims to determine the prevalence and diagnostic value of skin manifestations of PAD. Methods: This was a cross-sectional descriptive study of consecutive adults with hypertension and diabetes attending the consultant medical outpatient department, University of Benin Teaching Hospital, Benin-city, Nigeria. Physical examination of the skin of the lower limbs for features suggestive of PAD and ankle-brachial index (ABI) were performed. A diagnosis of PAD was made if ABI < 0.9. Results: Of the 541 participants, 115 (21.3%) had skin changes suggestive of PAD, and 182 (33.6%) had low ABI < 0.9. Among participants with PAD, 65 (35.7%) had skin manifestations suggestive of PAD. The association between PAD and skin manifestations suggestive of PAD was significant ($\chi^2 = 34.248, P < 0.001$). The sensitivity, specificity, positive, and negative predictive values of the presence of skin manifestations as a diagnostic tool for PAD compared with low ABI was 35.7%, 86.1%, 56.5%, and 72.5%, respectively. Conclusion: Among participants with PAD, the prevalence of skin manifestations of suggestive of PAD was 35.7%. Reliance on the presence of skin changes for diagnosis of PAD may result in missed or delayed diagnosis because of its low sensitivity and positive predictive value.

Keywords: Adults, diabetes, hypertension, peripheral artery disease, skin

Introduction

Peripheral artery disease (PAD) is a noncommunicable disease of growing public health importance. PAD, together with stroke and coronary heart disease, make up the cardiovascular triad. Although PAD shares similar risk factors and mortality concerns with coronary artery disease and stroke, it receives less attention. For the most part, PAD remains underdiagnosed, especially in the general population.1 PAD is however not uncommon among persons with established cardiovascular risk factors, particularly among the elderly, smokers, and persons with type 2 diabetes mellitus. In Nigeria, the prevalence of PAD among persons with hypertension and type 2 diabetes mellitus range between 24.8%–41.8%2–3 and 22.0%–52.5%,4–7 respectively.

The attendant diminution in the blood supply to the lower limbs contributes to the skin changes seen in PAD. Lower limb ischemia accounts for more than half of the foot lesions seen in patients with diabetes.8,9 Skin manifestations of PAD include a change in skin color, cold, dry, and atrophic skin, loss of hair, dystrophic nail changes, and fissures.10 Other dermatological features of PAD include proneness to skin infections, ulcerations, poor wound healing, gangrene, and ultimately limb loss. Although PAD is a relatively rare indication for lower limb amputation, the survival rates following nontraumatic amputations from vascular etiology are low.11–13 Indeed, the death rate in patients with PAD is notably increased if foot ulcerations, infection, or gangrene occur. By the time PAD becomes clinically manifest, it may need pricey resources to improve the circulatory health of the limb.

There is, however, limited documentation of observed skin manifestations of PAD in the literature. This paper aims to describe the frequency and forms of skin changes suggestive of chronic ischemia in a cohort of Nigerian medical outpatient clinic attendees with hypertension and/or type 2 diabetes mellitus. The utility of the presence of skin manifestations suggestive of chronic ischemia as a diagnostic tool for PAD was also determined.

Methods

The study was conducted at the consultant medical outpatient department of the University of Benin Teaching Hospital, Benin-city, Nigeria. This was a cross-sectional descriptive study of consecutive adults with hypertension and diabetes attending the consultant medical outpatient department, University of Benin Teaching Hospital, Benin-city, Nigeria. Physical examination of the skin of the lower limbs for features suggestive of PAD and ankle-brachial index (ABI) were performed. A diagnosis of PAD was made if ABI < 0.9. Of the 541 participants, 115 (21.3%) had skin changes suggestive of PAD, and 182 (33.6%) had low ABI < 0.9. Among participants with PAD, 65 (35.7%) had skin manifestations suggestive of PAD. The association between PAD and skin manifestations suggestive of PAD was significant ($\chi^2 = 34.248, P < 0.001$). The sensitivity, specificity, positive, and negative predictive values of the presence of skin manifestations as a diagnostic tool for PAD compared with low ABI was 35.7%, 86.1%, 56.5%, and 72.5%, respectively. Among participants with PAD, the prevalence of skin manifestations of suggestive of PAD was 35.7%. Reliance on the presence of skin changes for diagnosis of PAD may result in missed or delayed diagnosis because of its low sensitivity and positive predictive value.

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Hospital (UBTH), Benin city, Nigeria, using a descriptive cross-sectional design. Consecutive study participants who met the inclusion criteria were recruited from the hypertension and diabetes clinics. To be eligible for the study, each study participant had either hypertension, type 2 diabetes, or both. Patients recruited from the hypertension clinic were adults aged 18 years and above with hypertension defined as blood pressure of $\geq 140/90$ mmHg or the use of antihypertensive drug(s) irrespective of blood pressure reading and presence of concomitant diabetes mellitus. Patients with type 2 diabetes mellitus aged 35 years and above who are not ketosis prone and who are on diet and/or oral anti-diabetic medications or insulin after several years of oral medication were recruited from the Diabetes Clinic irrespective of their glycaemic control and presence of concomitant hypertension. Potential participants who were pregnant or had type 1 diabetes mellitus, significant pitting pedal edema, bilateral lower limb amputation, or were not willing to partake in the study were excluded.

The study was conducted according to the Helsinki Declaration after obtaining formal ethical approvals from the UBTH’s Ethics and Research Committee (ADM/E.22 A/VOL. VII/159, ADM/E.22 A/VOL. VII/187).

Each study participant had a structured questionnaire administered. Obtained data included demographic profile and history of vascular surgery and lower limb amputation. History of intermittent claudication was assessed using an adapted Edinburgh Claudication Questionnaire. The resting blood pressures were measured from the right arm of the patients in a sitting position thrice at an interval of 5 min, and the average value was recorded in mmHg. The weight in kilograms and height in meters were measured using a stadiometer after patients were asked to remove heavy outer clothes, head dressings, and footwear. Each study participant was then asked to lie supine on an examination couch with the lower limbs exposed up to the knees. A thorough physical examination (visual inspection and palpation) of the feet and legs to identify skin manifestations suggestive of chronic lower limb ischemia was carried out after that. Abnormal skin appearance suggestive of chronic lower limb ischemia was noted if any of the following: dystrophic nail changes, cold feet, loss of hair, smooth and shiny skin, hyperpigmentation, ulcer, and gangrene were present in either lower limb. The pedal pulses (dorsalis pedis and posterior tibial arteries) were also palpated for their presence and adequacy. The occurrence of reduced or absent pedal pulses in at least one lower limb was noted as suggestive of PAD.

Next was the determination of the ankle-brachial index (ABI). Systolic blood pressures (SBP) at the ankles and the arms were measured using an 8-MHz hand-held Doppler (Summit Doppler Systems, Inc. Colorado, USA) and an Accoson® mercury sphygmomanometer. The cuff of the sphygmomanometer was applied just above the medial malleolus, and the Doppler probe was used to obtain signals from either the dorsalis pedis or posterior tibial arteries, depending on which had a better Doppler signal. The cuff was then inflated until the Doppler signal disappeared and gradually deflated for it to reappear. The pressure at which the Doppler signal first reappears is the ankle SBP. For the arm SBP, the cuff of the sphygmomanometer was applied about 2.5 cm above the base of the antecubital fossa, and the Doppler probe was used to search for the Doppler signal from the brachial artery. As with the ankle SBP, the cuff was inflated until the Doppler signal disappeared and gradually deflated to obtain the arm SBP. The ABI was then calculated by dividing the SBP from each ankle by the higher of the two-arm SBP. PAD is diagnosed if ABI is $<0.9$. Mild, moderate, and severe PAD was defined as ABI of 0.70–0.89, 0.40–0.69, and $<0.40$, respectively.

Each study participant had venous blood sample drawn for fasting blood sugar and fasting serum lipid profile levels. The laboratory investigations were done using the colorimetric method at the Chemical Pathology laboratory of UBTH, Benin-city.

Data analysis

Percentages, means, and standard deviation (SD) were used to summarize numerical variables. The Chi-square test was used to test the association between categorical variables. The sensitivity, specificity, positive, and negative predictive value of skin manifestations suggestive of chronic limb ischemia as a diagnostic tool for PAD was ascertained. The level of statistical significance was set at $P < 0.05$.

Results

A total of 541 adults participated in the study, of which 347 (64.1%) were females. The mean age ($\pm$ SD) of the study population was 58.38 ($\pm$ 4.57) years. More than half (51.8%) of the study population had both diabetes and hypertension, while the others had either hypertension (22.2%) or diabetes (26.1%) only. None of the study participants has ever had coronary artery bypass graft or any other vascular surgery. Nine (1.7%) of the respondents had unilateral lower limb amputation, of which seven (77.8%) were from a nontraumatic cause.

About one-fifth (115/541) of the study population had abnormal skin appearance suggestive of chronic lower limb ischemia. Trophic changes were the most frequently encountered abnormality. More than half of the study participants had more than one skin abnormality suggestive of lower limb ischemia. Table 1 shows the distribution of the observed skin abnormalities.

Thirty-three (6.1%) of the study participants had intermittent claudication. Of the 115 study participants with abnormal feet appearance, 12 (10.4%) had a positive history of intermittent claudication. The association between a history of intermittent claudication and the presence of skin manifestations suggestive of chronic lower limb ischemia was statistically significant ($\chi^2 = 4.792$, df $= 1$, $P = 0.029$).

Seventy (12.9%) of the study population had reduced or absent dorsalis pedis and posterior tibial artery pulsations in at least one lower limb, of which 51 (72.9%) also had abnormal feet appearance. The association between the presence of reduced or absent pedal pulses and skin manifestations suggestive of chronic lower limb ischemia is statistically significant ($\chi^2 = 127.898$, df $= 1$, $P < 0.001$).
About one-third (182/541) of the study population had PAD diagnosed by a low Doppler-derived ABI (<0.9) in at least one limb. Among study participants with low ABI, 25 (13.7%) had symptomatic PAD and 55 (30.2%) had reduced/absent pedal pulses. The proportion of study participants with skin changes suggestive of chronic limb ischemia was higher among those with low ABI (<0.9). This observation was significant except for foot/leg ulcers as shown in Table 2.

About one-third (65/182) of the study participants with PAD diagnosed by a low ABI (<0.9) had abnormal feet appearance suggestive of chronic lower limb ischemia [Table 3]. The association between the presence of PAD diagnosed by a low ABI (<0.9) and the presence of skin manifestations suggestive of chronic lower limb ischemia is statistically significant ($\chi^2 = 34.248$, df = 1, $P < 0.001$).

Assuming Doppler-derived low ABI < 0.9 was the gold standard for screening for the presence of PAD, diagnosis of PAD using the presence of abnormal foot appearance suggestive of lower limb ischemia had a sensitivity of 35.7%, specificity of 86.1%, positive predictive value of 56.5%, negative predictive value of 72.5%, and likelihood ratio positive of 2.57.

Among the 182 study participants with PAD diagnosed using low ABI <0.9, 114 (62.6%), 51 (28.0%), and 17 (9.3%) had mild (ABI: 0.70–0.89), moderate (ABI: 0.4–0.69), and severe (ABI <0.4) PAD, respectively. The presence of skin changes suggestive of chronic limb ischemia was observed in 23 (20.2%), 32 (62.7%), and 10 (58.8%) of study participants with mild, moderate, and severe PAD, respectively. The association between the severity of PAD and presence of skin manifestations of PAD was statistically significant ($\chi^2 = 31.130$, df = 2, $P < 0.001$).

The relationship between biophysical characteristics and foot appearance is shown in Table 4. The mean age, ABI, and body mass index of study participants with feet appearance suggestive of chronic ischemia were significantly different from those with normal feet appearance.

**Discussion**

Although it is common knowledge that PAD may be associated with skin changes, there is a dearth of literature on the prevalence and diagnostic utility of cutaneous manifestations of chronic lower limb ischaemia. This is the first study known to author that compared the diagnostic utility of the presence of skin changes suggestive of chronic lower limb ischemia with low ABI (<0.9) among adult Nigerians with hypertension and diabetes mellitus.

Skin manifestations suggestive of chronic lower limb ischemia were observed in one-fifth of the study population. More than half of the respondents with these skin manifestations had multiple skin changes. Observed skin changes were more prevalent among older study participants, those with multiple cardiovascular risk factors and those with severe PAD (ABI <0.4). The study participants with skin changes suggestive of chronic lower limb ischemia had a significantly higher mean age compared to those without skin manifestations suggestive of PAD. The relationship was not surprising as advancing age is an important and independent risk factor for PAD.\(^{[3,5]}\) Skin manifestations suggestive of chronic ischemia was more prevalent among study participants with concurrent hypertension and type 2 diabetes (26.8%) compared with those with either hypertension (13.3%) or diabetes (17.0%). This was also not surprising as the risk for PAD increases many folds in the presence of multiple risk factors in an individual.\(^{[16]}\)

In this study, a lower mean ABI was observed among those with skin manifestations of chronic ischemia compared to those with normal skin appearance. Indeed, more than half of the patients with skin changes suggestive of chronic

### Table 1: Frequency of skin changes suggestive of chronic lower limb ischemia

| Skin changes on the lower limbs suggestive of chronic ischemia | Frequency (n=115) | HTN (n=16) | DM (n=24) | HTN/DM (n=75) |
|--------------------------------------------------------------|------------------|------------|-----------|---------------|
| Fissure                                                      | 36 (31.3)        | 4 (25.0)   | 9 (37.5)  | 23 (30.7)     |
| Hyperpigmentation                                            | 49 (42.6)        | 6 (37.5)   | 11 (45.8) | 32 (42.7)     |
| Trophic change                                               | 54 (47.0)        | 8 (50.0)   | 7 (29.2)  | 39 (52.0)     |
| Cold skin                                                    | 26 (22.6)        | 1 (6.25)   | 4 (16.7)  | 21 (28.0)     |
| Ulceration                                                   | 19 (16.3)        | 1 (6.25)   | 4 (16.7)  | 14 (18.7)     |

*Multiple skin change noted in 55.6% of study group. HTN=Hypertension, DM=Diabetes mellitus

### Table 2: Association between presence of skin changes suggestive of lower limb ischemia and low Doppler-derived ankle brachial index <0.9

| Skin changes on the lower limbs suggestive of chronic ischemia* | Low ABI (n=182), n (%) | Normal ABI (n=359), n (%) | $\chi^2$ | $P$ |
|---------------------------------------------------------------|------------------------|---------------------------|---------|-----|
| Fissure                                                       | 22 (12.1)              | 14 (3.9)                  | 13.036  | <0.001|
| Hyperpigmentation                                             | 28 (15.4)              | 21 (5.8)                  | 13.330  | <0.001|
| Trophic changes                                               | 35 (19.2)              | 19 (5.3)                  | 26.113  | <0.001|
| Cold feet                                                     | 22 (12.1)              | 4 (1.1)                   | 31.790  | <0.001|
| Foot/leg ulcers                                               | 10 (5.5)               | 9 (2.5)                   | 3.181   | 0.074|

*Multiple skin change noted in 55.6% of study group. ABI=Ankle brachial index
lower limb ischemia had low ABI (<0.9). However, only about one-third of the patients with PAD diagnosed by Doppler-derived ABI <0.9 had skin changes suggestive of chronic lower limb ischemia. Thus, the prevalence of skin manifestations suggestive of PAD was 35.6% in this study. This was not a chance observation. The association between skin manifestations suggestive of chronic lower limb ischemia and the presence of PAD diagnosed by low Doppler ABI was statistically significant.

All forms of skin manifestations suggestive of chronic lower limb ischemia observed in this study were significantly higher among study participants with PAD diagnosed by low ABI (<0.9) except for foot/leg ulcers.

A significantly higher proportion of study participants with moderate and severe PAD had skin changes suggestive of chronic lower limb ischemia compared with those with mild PAD. However, dependence on skin changes suggestive of lower limb ischemia to make a diagnosis of PAD had low sensitivity and low positive predictive value. Other studies have shown that the presence of skin manifestations of chronic lower limb ischemia is neither necessarily specific nor sensitive for diagnosing PAD.[15-20]

This study further supports the added value of using ABI as a screening tool for PAD.[21-23] Reliance on clinical examination of the lower limbs for skin changes, reduced pulses, or presence of intermittent claudication as means of diagnosing PAD are likely to miss mild PAD.[22,23] Early diagnosis of PAD has therapeutic advantage as low ABI is considered as a coronary disease equivalent. Indeed, the risk of adverse cardiovascular events from PAD far outweighs the risk of skin changes and even limb loss.[24]

This study is limited in not having angiographic confirmation of PAD. More than three-quarters of the study population have diabetes mellitus. The foot/leg ulcers encountered in this study may not be wholly attributable to PAD as the presence of peripheral neuropathy, which may also contribute to the observed foot ulcerations, was not excluded in this study. In the same vein, other observed skin changes may be part of cutaneous manifestations of diabetes mellitus which are not necessarily due to chronic limb ischemia.[8,9]

**Conclusion**

The prevalence of skin manifestations of PAD was 35.7% in this study and was higher among those with ABI <0.7, indicating moderate and severe PAD. It is important to note that the absence of skin manifestations of PAD does not preclude the diagnosis of PAD. The low sensitivity and low predictive value of skin changes suggestive of chronic lower limb ischemia make it a limited diagnostic tool for PAD. Indeed, reliance on the presence of skin changes to make a diagnosis of PAD may result in a delayed or missed diagnosis. Thus, routine periodic determination of ABI among individuals with established cardiovascular risk factors such as hypertension and diabetes mellitus is recommended.

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**Conflicts of interest**

There are no conflicts of interest.

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