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Review Article

Screening and Diagnosis of Peripheral Arterial Disease in Patients with Diabetes: Current Perspectives

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Abstract

Peripheral Arterial Disease (PAD) is a world-wide concern, especially in persons living with diabetes. This is a challenging condition since often it is asymptomatic and when symptoms do set in, they could be indicative of advanced disease. The early detection of PAD is important as this enables its early management through lifestyle changes and other non-invasive medical modalities. However, there are various issues related to diagnosing PAD especially at primary care level since there are significant issues relating to diagnostic accuracy that could affect the timely diagnosis of this condition.

A clinical assessment tool is only of value if the interpretation of the results is correct and repeatable, which is the main issue relating to the clinical tests outlined in this paper. Although literature highlights the importance of accurate screening, diagnosis and management of PAD, this paper provides evidence from studies on the importance of using different non-invasive modalities when assessing patients with PAD. The authors suggest that when results do not concur, further extensive evaluations should be performed. Such information will alleviate the burden related to PAD and its complications. This paper compares the application of different physiological tests used for the early identification of PAD.

Keywords: Peripheral Arterial Disease; Diabetes Mellitus; Diagnosis; Screening

Background

Peripheral Arterial Disease (PAD), a condition characterized mainly by reduced blood flow, is a significant and common co-morbidity in diabetes mellitus. There is no doubt that people living with diabetes mellitus and PAD represent a special subgroup of patients. They tend to have different clinical manifestations, natural history and outcomes than those persons living with PAD without the complication of diabetes. Patients frequently present with significant skin tissue loss without significant symptoms which rapidly progress to limb loss [1] thus the importance of this review is to highlight issues relating to the screening and correct diagnosis of PAD at a timely and prompt manner.

It is known that around the world every 30 seconds a lower limb is lost to diabetes [2]. PAD may be harder to detect in diabetes than in persons living without diabetes because of a number of potential issues that may mask the condition, namely arterial wall calcification and neuropathy. Thus, to improve outcomes by early diagnosis of PAD, it is imperative that the majority of health care professionals who manage patients living with diabetes on a regular basis are well informed of these potential issues relating to the

examination and timely diagnosis of this condition since "time is tissue" [3] consequently the longer the delay in diagnosing PAD, the more the potential for limb loss due to complications such as diabetic foot ulceration. Thus, this paper will focus on the various issues relating to PAD in the patient with diabetes, highlighting the various difficulties and possible deficits in the diagnostic process, that may be encountered and how these may be possibly overcome to ensure the prompt identification of PAD, most importantly, in the asymptomatic patient, where the clinician may have the greatest difficulties regarding the diagnostic process.

PAD, the gradual or complete occlusion of arteries due to formation of atherosclerotic plaques [4] is one of the major complications of diabetes mellitus of worldwide concern. PAD affects the lower extremities more commonly than the upper extremity vessels [5]. Persons living with diabetes have a 2/3 fold increased risk of developing atherosclerosis [6]. For every 1% increase in HbA1c, there is a corresponding 26% increased risk of developing PAD [7]. This condition poses more concern since approximately half the individuals living with PAD remain undiagnosed since it may be asymptomatic [8] and only after major complications manifest themselves will this condition be diagnosed and addressed.

It is important to note that:

- The femoral and popliteal arteries are affected in 80 - 90% of symptomatic PAD patients [9].
- Prevalence of amputation in PAD patients is 3 - 4% [10].
- It is estimated that > 200 million people have PAD worldwide [5].
- Risk of PAD increases with age, being quite uncommon in the young population [11].
- 20% to 30% of individuals with PAD have DM [12].
- It is estimated that in industrialized countries, 50% of people living with diabetes and foot ulceration have underlying PAD [13].
- Only about 30% of persons diagnosed with PAD live up to 15 years after initial diagnosis [14].
- A long term follow-up of patients with symptomatic PAD indicated that approximately 30% will experience a cardiovascular event within 5 years [15].

All these facts highlight the need of addressing PAD in a timely manner to decrease the incidence of morbidity and mortality in this specific group of patients. For these reasons, the early detection of PAD is of paramount importance if the severe complications, including systemic complications leading to diabetic foot ulceration, amputations and cardiovascular risk [16] are to be avoided.

Lower limb morbidity is worse in symptomatic PAD when compared with those without symptoms. A long term follow up study reported a cumulative incidence of PAD deterioration over 5 years of 7% in patients with asymptomatic PAD, while for patients with intermittent claudication, the 5 year cumulative incidence for PAD deterioration was 21% [17]. PAD symptoms may include numbness, weakness, sensation of coldness and possibly ulceration. These symptoms severely affect a patient's ability to walk or exercise, mainly causing painful cramping in one of both hips, thighs or calf muscles, thus leading to an associated reduced quality of life [18]. Symptoms of PAD can resolve spontaneously, remain stable for several years or may progress rapidly to develop critical limb ischaemia [19].

Diagnosis of peripheral arterial disease

Approximately 80% of patients with PAD are asymptomatic and it is estimated that about 20-35% complain of intermittent complications [16]. Patients may be undiagnosed for two main factors: either because the individual is asymptomatic or has atypical symptoms or because unfortunately health professionals may make use of poorly validated methods of screening for PAD; i.e. pulse palpation and history of intermittent claudication [20]. Patients with neuropathy may not experience intermittent claudication because of nerve dysfunction [21]. Thus it should be kept in mind that the absence of intermittent claudication will not necessarily imply normal vascular perfusion in these subgroup of patients.

Furthermore, during clinical assessment, the skin manifestations attributed to PAD including changes in colour, pallor, cyanosis, extreme change in temperature gradient, loss of hair and dystrophic nail anomalies and atrophic, shiny dry skin must also be noted. Other dermatological features related to PAD may include fissures, skin infections, ulcerations and poor healing.

Clinical assessment for vascular perfusion

There are several modalities in order to assess for PAD. Scientific literature recommends 6 most commonly tests especially used at primary care level [22].

Foot pulse palpation

A pulse is defined as the pressure wave generated by ventricular contraction and relaxation during the cardiac cycle [2]. This is a means of clinically determining arterial inflow to the lower limbs. The dorsalis pedis and posterior tibial arteries are the two most commonly palpated arteries. In the foot, pulses are usually denoted as present or absent, with absent pulses denoting the presence of PAD.

Foot pulse palpation is reported as having a sensitivity of 55% and a specificity of 60% for diagnosing PAD [23]. One critical issue is that early signs of PAD cannot be detected using this method on its own. This should raise awareness on the use of other means of assessing for vascular perfusion. This limits the use of pulse palpation in the clinical setting; namely one can rely only on absence of a foot pulse to highlight the presence of PAD.

Ankle brachial pressure index (ABPI)

The Ankle Brachial Pressure Index is a ratio of the systolic pressure at the brachial artery in the arm to the systolic blood pressure at the ankle. The index is calculated by dividing the systolic blood pressure at the ankle by the systolic blood pressure at the arm. The patient must be placed in the supine position, having all tight clothing undone. If not taken in the supine position, there is the possibility of over-estimating by about 0.3 [24]. A doppler ultrasound and a sphygmomanometer are necessary to carry out this procedure.

This is a commonly used tool for the non-invasive assessment for PAD. Although studies have shown a sensitivity of 90% and specificity of 98% for detecting haemodynamically significant stenosis, ABPI has its known issues. ABPI is unreliable in patients with arterial calcification since it is known to produce falsely elevated ankle pressure, giving false negative results, especially amongst patients with diabetes [25]. This is due to the hardness of the arterial walls resulting from calcification, making compression of the vessel only possible at higher pressures applied by the cuff. In addition, the ABPI has been shown to underestimate the presence of media calcification compared with findings from imaging techniques such as spectral doppler waveform analysis, toe brachial pressure index or duplex scanning [26].

ABPI values between 0.9 and 1.3 are considered as normal. Those values below 0.5 indicate severe arterial disease, values between 0.5 and 0.8 suggest the presence of arterial disease, whilst according to European guidelines, an ABPI value above 1.4 indicates arterial wall stiffening, which is associated with an increased risk of cardiovascular events [11].

Practitioners interpreting ABPI results should be cautious in their interpretations. Although the literature suggests that values between 0.9 and 1.3 should be considered as normal, in patients with arterial calcification, an artefactually high result could be present even though results could indicate normality. Thus, it stands to reason that in the patient with diabetes, an ABPI result falling within the normal range does not necessarily imply normal vascular perfusion, especially in the presence of adjunct clinical signs and symptoms associated with impaired vascular perfusion. Indeed, it may be relied upon only when results indicate PAD (< 0.9) or when above 1.4. In these cases, the ABPI result would be alerting the clinician on the possibility of the presence of PAD, thus instigating the need for further investigations such as duplex scanning.

Toe brachial pressure index (TBPI)

TBPI differs from ABPI in that pressure of the toe is utilized for calculating the ratio instead of the ankle arteries. This is because the toe vessels are less susceptible to vessel stiffness, which makes the TBI useful [27]. Studies have shown that 14% to 27% of patients referred for distal pressure measurements have a low TBI but a normal ABPI [28] confirming the effect of arterial intima calcification on ABPI results. A TBI value between 0.5 to 0.75 is considered as normal [29] whilst a TBI < 0.2 is considered severely ischemic and diagnostic of critical limb ischemia [30].

Up to a few years ago, reliable measurement of TBI was limited to vascular laboratories due to costly equipment and time-consuming techniques [31]. However, nowadays hand-held doppler units which can also utilize a photopletysmography (PPG) probe are well within the financial reach of most clinicians, making this diagnostic modality a possibility in most clinics.

The method of obtaining this ratio is similar to the ABPI, however with a suitable cuff being administered around the big toe instead of the ankle. A PPG probe or an ultrasound probe is utilized to determine the point when the digital artery is closed by the applied pressure. The ratio of the brachial to the toe pressure is calculated

by dividing the Toe Pressure with the Brachial Systolic Pressure. The TBPI has been reported to have varying degrees of sensitivity ranging from 45% to 100% and specificity from 16% to 100%, depending on the population studied. Overall, the TBI has good test performance in patients with diabetes, claudicants and those at risk of PAD, and therefore may be a useful adjunct for vascular screening in these cohorts [29].

Spectral doppler waveform analysis

This diagnostic modality involves the use of a doppler with a screen readout that allows the clinician to interpret the shape of the waveform and thus assess haemodynamics. Waveforms can be triphasic, denoting normal blood flow; biphasic, denoting early stage PAD, or monophasic denoting a more severe form of PAD (Figure 1). Sensitivity and specificity of doppler waveform analysis are unaffected by diabetes diagnosis, with a sensitivity of 82.76% and specificity of 88.33% when utilizing angiography as the reference standard [32]. Interrater reliability of the spectral Doppler waveform interpretation has been reported as excellent ($\alpha = 0.98$). The intraclass correlation coefficient showed a high degree of correlation in waveform interpretation across raters ($P < .001$) [33].

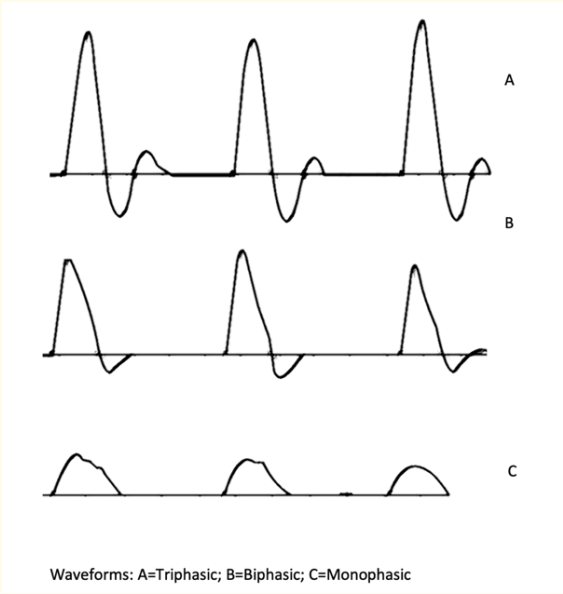

Figure 1: Depicting the different types of waveforms output by the hand held doppler.

Whilst a few decades ago this examination was only possible utilizing bulky and expensive ultrasound machines, hand-held dopplers nowadays can have this functionality, making this modality available to practitioners who may not be necessarily ultrasonography specialists. Whilst this may have some limitations - most notably training - this opens the possibility of easier accessibility since the majority of clinicians with sufficient training can utilize this technique, thus resulting in a higher impact on the number of patients that can be screened and thus identified at an early stage of the disease. Formosa and co-authors [33] have demonstrated that experienced clinicians have high inter-rater reliability when interpreting spectral waveform analysis, which is very encouraging to disseminate this modality amongst practitioners. This is possible for various reasons, namely:

- Availability of equipment to a wider range of clinicians
- Less expensive equipment necessary
- Less cumbersome and less time-consuming techniques for patient examination
- Less effected by calcification.

Absolute toe pressures (ATP)

ATP is claimed to be a reliable [34] non-invasive, time and cost-efficient tool. A study concluded that ATPs are useful to assist in diagnosing PAD in clinical practice, however, results should be interpreted with caution due to the small probability of PAD being present with a negative test [29]. In general, a toe pressure of 70 to 110 mmHg is considered normal and any value below is diagnostic of PAD. A toe pressure < 30 mmHg requires immediate referral to a vascular team [29] and wound healing potential drops as ATP decreases from the normal values.

Transcutaneous oxygen perfusion (TcP02)

TcP02 is important when one wishes to assess macrocirculation and microcirculation of the skin, i.e. the amount of oxygen circulating in the blood capillaries [35]. This non-invasive approach is unaffected by calcified arteries and a higher pressure reading clinically correlates with increased wound healing potential. Clinicians may obtain specific information relative to leg ischemia, wound healing potential, optimal amputation level and incision site determination for the lower extremities [30]. Electrodes are spaced on the skin in the area of interest avoiding callus, oedema and bony prominences and it reveals whether the blood vessels are damaged

or blocked. The sensor warms the surrounding skin, causing localised hyperaemia and facilitating oxygen diffusion. A normal healthy value in the foot is > 50 mmHg. A value of < 40 mmHg is thought to represent sufficient hypoxia to impair wound healing [36]. According to International Working Group on the Diabetic Foot [IWDGF] guidelines of 2019, in a result < 25 mmHg, urgent vascular imaging should be considered together with revascularization [1].

TcP02 is comprised of various measures which includes local tissue perfusion pressure, local oxygen consumption, arterial oxygen content, arterial pressure and neurovascular function [35]. It reflects very well the metabolic state of the lower limbs. TcP02 is being currently used in the management of vascular diabetic foot disease [37]. Since it is not affected by arterial calcification, it has obvious advantages over ABPI. Indeed this modality has been reported to be a better predictor of major adverse cardiovascular events than ABPI. TcPo2 is also a complement to macrocirculatory investigations in the prediction of the outcome of chronic foot ulcers. It has been reported that the sensitivity, specificity, positive predictive value and negative predictive value were 100%, 85.2%, 38% and 100% respectively [38].

Diabetes foot screening guidelines related to PA

PAD presents a high social, health and human impact. As a result, early identification and prevention of the disease is of great significance in order to reduce the impact of PAD and the risk of amputation. In the patient with diabetes, preventive measures are more cost effective than the need for surgical interventions and rehabilitation [39]. Thus, necessitating early screening to detect the presence of PAD and to monitor individuals living with PAD.

Currently, IWGDF guidelines still advocate the use of pulse palpation together with a relevant medical history as a minimum when assessing for PAD, although the quality of evidence behind this recommendation is low according to the authors themselves. Furthermore, they advocate to perform at least a pedal waveform analysis in combination with ABPI and absolute toe pressures or TBPIs since there is no single modality has been shown to be optimal and there is no definite threshold value at which PAD can be reliably excluded. However, PAD is a less likely diagnosis in the presence of ABPI 0.9 - 9.3, TBPI > 0.75 and triphasic pedal waveforms. Although this is a strong recommendation, the authors confirm that the quality of evidence behind this recommendation is low [1]. Figure 2 lists recommendations from the IGWDF guidelines.

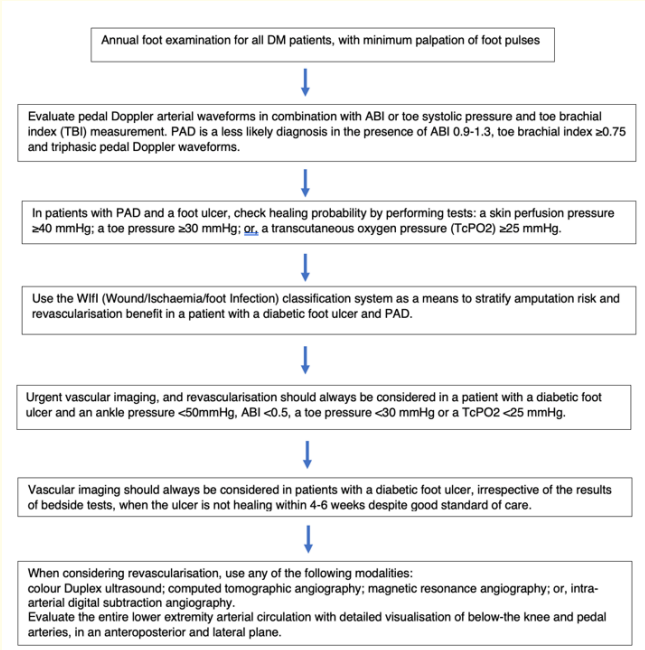

Figure 2: Vascular foot screening for PAD in diabetes, adapted from the IWGDF guidelines.

Whilst there is currently a significant amount of literature regarding PAD, the same methods of assessment have been used amongst the majority of health care practitioners, for over 20 years [40]. Currently there is a lack of consensus regarding the most accurate method of assessment [41]. Most of the guidelines advocate the use of foot pulse palpation, but the evidence grading for this recommendation is poor [42]. ABPI presents a further challenge when calcification (Monkberg's disease) is present, resulting in artifactually elevated results. Thus, the actual presence of PAD may be overlooked, since this test could yield a false negative result.

Screening is the key to detecting early-stage disease and allows the initiation of optimal preventive medical treatment, which may reduce modifiable risk factors for patients at risk for arteriosclerotic disease [43]. An emerging modality that in the future could have an impact on detection of PAD is medical thermography, which has been shown to detect higher forefoot temperatures associated with this condition in type 2 diabetes mellitus [44,45].

Other methods of detecting PAD

Besides the most commonly used methods to assess patients for PAD, there are other methods that may be employed, however these are often utilized at a hospital or more specialized level.

Studies with non-invasive techniques include hyperspectral imaging (HSI), laser Doppler perfusion imaging (LDPI), laser speckle contrast imaging (LSCI), near-infrared (NIR) spectroscopy (NIRS), spectrophotometry and vascular optical tomography imaging (VOTI).

Other diagnostic techniques that focus on assessing the microcirculation of the skin or muscle in the lower extremity and use contrast agents, include magnetic resonance perfusion imaging, contrast-enhanced ultrasound and NIR fluorescence imaging with indocyanine green [46].

Computed Tomography Angiography (CTA), Magnetic Resonance Angiography and Duplex Ultrasonography are found in specialized imaging departments, often employed to determine the exact location of vessel blockage and level or type of surgery is required in order to treat PAD. However, the issue of heavily calcified vessels in patients with diabetes may also present a diagnostic challenge when using duplex US or CTA, as the calcification may result in an obscured arterial lumen and inability to reliably diagnose the degree of PAD [47].

Discussion

PAD is often asymptomatic and therefore should be assessed in every diabetic patient [37], as highlighted by the majority of clinical guidelines. Currently, ABPI is the most employed test in order to diagnose PAD, however its value in the diabetic patient is questionable because of arterial calcification which is known to produce false negative tests results.

There is confounding evidence that today the best tool to diagnose PAD has not been established, with very little agreement between the above six tests [22]. Thus, practitioners should be aware of the various inconsistences between tests and possibly be advised to use concurrent alternative methods of diagnosis following more detailed clinical evaluation. When the results of the various non-invasive modalities employed do not concur, more sophisticated imaging modalities such as duplex scanning or angiography should be considered.

Authors postulate that one of the major reasons of the increasing amputation rate in diabetes could be attributed to untimely identification of PAD due to asymptomatic presentation or incorrect diagnosis resulting from inconsistencies exhibited between the various tests [48].

Applying latest research to actual clinical practice, especially at a primary level, may be the link to instilling the notion that early detection is better than cure in order to help save more limbs by detecting PAD at an earlier stage and thus instigating early non-invasive management which has been shown to be effective in reducing the impact of this condition. Early treatment for PAD should focus on reducing symptoms and preventing further progression of the disease, including calf muscle stimulation [49]. Lifestyle changes (smoking cessation, diet, diet low in saturated and trans fat), physical activity and claudication medication being often sufficient to slow the progression or even reverse the symptoms of this condition [50].

With longer life expectancy, the prevalence of PAD is increasing, presenting an important health challenge [51]. As a result of this longer life expectancy, an increase in prevalence was observed between the years 2000 - 2010 resulting in an estimated affected number of more than a quarter of a billion people worldwide, of whom 40 million were in Europe [52].

PAD is still poorly understood by the general public and underdiagnosed in primary care, especially in asymptomatic patients, leading to under treatment of the condition [16]. Limited exposure to PAD, its risk factors, preventive measures and complications in medical school curricula have also been associated with sub optimal knowledge of general practitioners with regards to identifying the clinical signs of the disease [53].

Conclusion

This paper highlights the need for all practitioners clinically responsible for diabetes patients, who are likely to present with PAD, to be made aware with regards to the importance of timely diagnosis of this condition. As highlighted, they should also be aware of the inconsistences which some clinical vascular tests pose, especially in the presence of peripheral neuropathy and calcification of arteries, thus the use of multiple tests is advocated when results do not concur. When presented with clinically challenging patients, they should be cautioned to utilize gold standard modalities for the

diagnosis of PAD such as duplex scanning. This could significantly reduce the number of patients living with diabetes who would falsely be identified as not having PAD and therefore denied beneficial and effective secondary risk factor control.

Conflict of Interest Statement

The authors declare no conflict of interest.

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