Screening of Peripheral Arterial Disease in People with Type 2 Diabetes Mellitus – A Commentary Article

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Abstract

Peripheral arterial disease (PAD) is a common diabetes-related chronic complication. An unmet need for limb salvage is an effective tool to identify the presence of PAD. Various strategies have been used to assess PAD in patients with diabetes. However, no universal consensus has been yet reached. Babaee et al. investigated the diagnostic accuracy of different non-invasive methods namely Plethysmographic-and-Doppler derived ankle brachial index, toe brachial index, and Pulse volume waveform analysis to identify PAD in people with type 2 diabetes mellitus (T2DM). The aim of this commentary is to discuss the current advances on evaluation of PAD in people with T2DM.

Keywords: Peripheral arterial disease, Ankle brachial index, Toe brachial index, Pulse volume wave analysis

Introduction

Peripheral arterial disease (PAD) is a prevalent form of atherosclerotic vascular disease in type 2 diabetes mellitus (T2DM). Diagnosis and treatment of PAD is more challenging in these patients. Presence of concomitant neuropathy masks typical pain symptoms, and typical criteria for intermittent claudication are not clearly met [1]. Moreover, PAD often affects the small arteries that makes effective revascularization less successful [2]. Thus, screening and early detection of PAD are of major importance in patients with T2DM.

Ankle- brachial index (ABI) is the most common non-invasive tool used for screening of PAD [3]. Population-based studies demonstrated that ABI ≤ 0.90 is diagnostic for PAD [3]. However, the diagnostic accuracy of ABI is lower in patients with diabetes compared to the non-diabetic individuals due to the medial artery calcification (MAC) [4,5]. On the other hand, Doppler-based ABI is a time-consuming and operator-dependent procedure [3]. To overcome these limitations, other non-invasive screening tools such as automated plethysmography-based ABI (ABI_{PLE}), toe brachial index (TBI), and pulse volume wave (PVW) analysis have been proposed [3,6]. The studies investigating the diagnostic performance of these non-invasive tools for detection of PAD were conducted in different populations using various standard methods leading to inconclusive results [6-8]. The diagnostic accuracy of these methods as well as the specific cut-off point for diagnosis of PAD is even less conclusive in patients with diabetes. Babaee et al. published a study in 2019 investigating the diagnostic performance of four tests widely available and applied for screening of PAD [9]. However, the generalization of the results and implication of the cut-off points for screening of PAD in patients with diabetes is yet to be investigated in more similar populations. The aim of this commentary is to evaluate this study and discuss updates in this research emphasizing the necessity for conducting more precise similar studies to explore the best screening tool with the most appropriate cut-off value for detecting PAD in patients with T2DM.

Ankle Brachial Index

Babaee et al. indicated that in a population of patients with T2DM, Doppler-based ABI ≤ 0.9 (ABI_{DOP} ≤ 0.9) could detect the significant (≥ 50%) arterial stenosis identified...
by ultrasound Doppler scan (UDS) with the sensitivity of 72.7%, and specificity of 95.8%. Receiver-operating curve (ROC) analysis of $\text{ABI}_{\text{DOP}}$ to determine the best cut-off value for detection of ≥50% stenosis identified by UDS in this population also determined the cut-off point of 0.9 as the best threshold [9].

$\text{ABI}_{\text{DOP}}$ has long been known as the first diagnostic method for screening of PAD [3]. Diagnostic accuracy of the ABI varies based on the population studied, the cut-off value, and the method used to detect flow [3]. However, $\text{ABI}_{\text{DOP}} \leq 0.9$, obtained from the studies assessed >50% stenosis identified by different imaging methods, including DUS, magnetic resonance angiography (MRA), or angiography, remains the most acceptable threshold [3,10-12]. Most of these studies found reasonably high specificity (89%–99%) but low sensitivity (69%–79%), with the lowest sensitivity in patients with DM [3]. Babaei’s study also confirmed the results of previous studies regarding the $\text{ABI}_{\text{DOP}} \leq 0.9$ as the best threshold for detection of PAD and also the lower sensitivity of this method in patients with DM. However, Doppler-derived ABI is an operator dependent procedure that needs experience and technical skills, particularly where different operators are involved [13,14]. Moreover, pre-test conditions such as variation in body position, recent smoking and caffeine intake, exercise, and pre-measurement rest time all are demonstrated to affect the ABI [15-19].

During the recent years a number of automated ABI devices have been developed which require little experience and do not need a rest period before measurements [6,20]. The majority of these devices use oscillometric technology to detect systolic blood pressure [20]. Several studies suggest an automated oscillometric method is comparable with standard handheld-Doppler method for detection of PAD [20,21]. It is a reliable, cost-effective, and less time-consuming method which can be used widely to measure ABI [20,21]. However, to increase the sensitivity to detect PAD using an oscillometric ABI, a higher threshold of 1.0 might be preferable [20]. Another alternative method is based on reperfusion plethysmography, named automated plethysmographic ABI. Several studies compared the diagnostic performance of this method with conventional Doppler method indicating lower diagnostic accuracy of automated plethysmographic-based ABI although it could be used as a fast method to identify at risk patients [6]. Moreover, the optimal cut-off point for diagnosis of PAD was considerably higher than the threshold of ≤0.9 which traditionally used [6]. Similarly, Babaei et al. indicated a lower diagnostic accuracy of plethysmographic-based ABI for detecting PAD in a population of patients with T2DM. They also showed that a higher threshold of $\text{ABI}_{\text{PLE}}$ could to some extent improve the sensitivity of this method [9]. This finding seems to be a common association with the use of the automated devices [6,9,20]. However, this improved sensitivity is in the expense of reduced specificity which results in diagnosis of more patients as having PAD and being referred for confirmatory test such as DUS which raises both ethical and financial issues. Thus, it is not clear whether the automated devices have sufficient diagnostic accuracy to be used to screen PAD in people with T2DM.

### Pulse Volume Waveform

Pulse wave analysis is another non-invasive, diagnostic procedure that can be utilized to evaluate blood flow in the extremities. Recently, oscillometric-or-plethysmographic-based devices combine fully automated ABI and pulse wave analysis to identify PAD [22,23]. Integrating these two diagnostic techniques within one device provides a highly accurate method for detection of PAD [22,23]. The study conducted by Babaie et al. also indicated that analysis of PVW has good sensitivity (81.8%) and high specificity (93.2%), with even a better sensitivity than ABI [9]. Results of these studies suggest pulse wave analysis either alone or in combination with ABI could be used in the primary care to safely reduce unnecessary secondary care referrals. Moreover, better diagnostic performance of PVW might be explained by the fact that the presence of calcified artery does not influence the pulse volume recording commonly seen in the patients with T2DM [7,24]. MAC occurs due to crystallization of calcium and phosphate in the medial layer of the arterial wall, making the vessels less compressible, leading to falsely normal or even high ABI [25]. This phenomenon is associated with elderly, hypertension, T2DM, and chronic kidney disease [25-27]. PVW has been shown to overcome the limitation of ABI in diagnosis of PAD in these conditions. It is recommended by the European Society of Cardiology (ESC) and the American Heart Association (AHA) to be used for further assessment in patients suspected to PAD with normal or high ABI [28,29]. However, this method has some limitations. PVW represents the total blood flow to the area under investigation. It does not identify where and to what extent a specific artery is occluded [30]. Moreover, cardiac output, vasomotor tone, patient motion, and heat-induced vasodilation may affect the recordings [30,31].

### Toe Brachial Index

Another alternative technique to identify falsely high ABI is TBI. Toe arteries are not commonly affected by MAC phenomenon [32]. Although many studies investigating the diagnostic accuracy of TBI indicated better performance of this method, especially in patients with diabetes, a wide range of sensitivity (45% to 100%) and specificity (16% to 100%) has been reported [33-35]. On the other hand, there is not a well-defined and evidence-based cut-off point for TBI to detect PAD. TBI <70 is recommended by several guidelines [36]. Babaei et al. further examined
the diagnostic accuracy of TBI for detection of PAD in a population of patients with diabetes. They concluded that the sensitivity of TBI<0.38 is 100%. Hence, it might be the best cut-off point to detect PAD in patients with T2DM [9]. However, they used UDS as the standard reference. Moreover, a hand-held Doppler device was applying for measurement of TBI. Despite the large heterogeneity observed in the diagnostic accuracy of TBI for diagnosis of PAD, EASD and AHA guidelines recommend TBI in cases with clinically suspected PAD but normal to high ABI [28,29]. However, normalized standard values need to be established in order to conclusively determine the diagnostic accuracy of this technique.

**Pedal Accelerated Time**

Non-compressible vessels or open wounds of the foot may preclude the use of ABI, or TBI measurements. In these cases, pedal accelerated time (PAT), direct duplex imaging of the pedal vessels which can provide real time physiologic information on pedal flow hemodynamics [37], is used to predict the limb salvage [38]. Applying this procedure in the vascular practice could be helpful in identification and treatment of patients with chronic limb threatening ischemia.

**Conclusion**

Babaei et al. explored diagnostic accuracy of various techniques namely ABI\_DOP, ABI\_PLE, TBI, and PVW for detection of PAD in a population of patients with T2DM. They concluded that PVW has the highest sensitivity (81.8%), followed by ABI\_DOP (72.7%), and ABI\_PLE (20%). Moreover, all methods showed excellent specificity. One of the limitations of this study was that the “gold standard” technique to identify PAD was duplex ultrasound imaging of lower extremity arteries. However, they used their own data to establish the best cut-off points for different techniques to detect PAD patients with T2DM. The results indicated TBI<0.38 is the best diagnostic test in this population.

The current literature also demonstrated that no single test reliably identifies PAD in patients with T2DM. ABI does not have sufficient diagnostic accuracy due to the MAC phenomenon. Although TBI can overcome this limitation and it is recommended to be used in patients with normal to high ABI, there is a large heterogeneity in diagnostic accuracy due to different population studied and various devices used to measure TBI. Moreover, there is not a well-established cut-off point for TBI to detect PAD. Furthermore, normal population studies and also studies using angiography as the gold standard are sparse. Given the rising number of patients with PAD and the shortcoming of the current methods, further studies are needed to validate the best non-invasive diagnostic tool for identification of PAD in people with T2DM.

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