

## REVIEW ARTICLE

# Clinical Symptoms Associated with Asymptomatic Peripheral Arterial Disease: A Literature Review

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## KEYWORDS:

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## ABSTRACT

**Background:** The incidence and prevalence of Peripheral Arterial Disease (PAD) is rising, yet physician awareness is insufficient. This review aims to increase awareness and detection of asymptomatic PAD in primary care, dermatologic, or podiatric practices through observable symptoms and subtle pathologies concomitant with PAD so patients may benefit from preliminary screening.

**Methods:** A systematic review of Google Scholar for literature establishing a link between PAD and observable symptoms or examinable pathologies that could be ascertained in primary care.

**Results:** 31 manuscripts were included. Four discussed examinable symptoms of PAD. Significant ORs predicted PAD by ABI < 0.9 for cool skin, cyanosis, or lower-extremity wounds or sores (6.4, 3.8, 6.0, respectively). Four papers described clinical tests, with diminished capillary refill time, venous filling time, unilateral absence of foot pulses, mild unilateral weakness in foot pulses (OR 8.6), auscultation of femoral bruit (OR 7.8), weak unilateral femoral pulse (OR 3.7), or absent and normal femoral pulses in opposite legs (OR 6.1) significantly predicting PAD. Four papers discussed PAD as an independent predictor of onychomycosis with risk odds-ratio (ROR) 4.8. Six papers investigated onychomycosis' relation to psoriasis, while another six mentioned psoriasis predicting PAD (OR 1.98; RR 2.6). Four studies demonstrated diminished peripheral nerve performance in PAD, and five mentioned PAD-related ulceration and the disease's ability to disrupt wound-healing (OR 2.31).

**Conclusion:** PAD is underdiagnosed, an issue that may be improved through increasing educational outreach awareness of the asymptomatic disease, and ability to detect subtle risk factors, symptoms, and pathologies predictive of PAD.

## ABBREVIATIONS

PAD: peripheral arterial disease

OR: Odds ratio

LR: Likelihood ratio

CLI: Critical limb ischemia

NCS: Nerve conduction study

SFA: Superficial femoral artery

DP: Dorsalis pedis (artery)

ABI: Ankle-brachial index

ROR: Risk odds ratio

RR: Relative risk

LEA: Lower extremity amputation

EMG: Electromyography

PCP: Primary care practitioner

PT: Posterior tibial (artery)

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## INTRODUCTION

Peripheral arterial disease (PAD) affects 8.5 million people in the US and is characterized by a loss or reduction of perfusion to the legs caused by atherosclerosis.<sup>1,2</sup> CDC and NIH data has demonstrated a correlation between risk of PAD diagnosis and age. As of 2016, PAD's prevalence has risen to an estimated 20% of individuals over 60.<sup>3,4</sup> Physician awareness and early diagnosis continues to be challenging largely because the majority of PAD cases are asymptomatic. Epidemiologic projections claim that PAD's prevalence is 27 million individuals in North America and Europe, 16.5 million of which are asymptomatic cases.<sup>5</sup> This literature review intends to increase awareness of clinically observable symptoms and more subtle associations for asymptomatic peripheral arterial disease that can be recognized in a primary care setting. Ideally, augmenting primary care physicians' ability to detect patients at-risk of PAD in conjunction with heightened ability to detect signs indicative of the disease through the patient interview and hands-on techniques may increase the patient's odds of a favorable outcome.

## METHODS

A search for relevant literature was carried out of Google Scholar in December 2017 and January 2018. Below are the specific keyword searches and aggregate number of results. Bracketed phrases were entered into Google Scholar's advanced search function, "with the exact phrase." All searches excluded publications before the year 2000. As a basis, the most recent 2016 AHA/ACC Guideline on the Management of Patients with Lower Extremity PAD (see reference 1) was included in the review, as was reference 2, the 2005 ACC/AHA Guidelines article due to the sheer number of sources citing this paper. When an article was read because it was referenced within one of the manuscripts brought up by these methods, it was also included in this review. For example, reference 11 was reviewed and cited, a source of reference 1.

Articles were included that mentioned peripheral arterial disease and any physically observable symptom or examinable pathology that could be determined in a primary care setting, along with research-based evidence supporting the link between PAD and this pathology.

**1. Include:** [peripheral arterial disease]; detection; awareness; dermatology; asymptomatic; symptomatic; risk factor; epidemiology.

Exclude: Asia; Africa. 48 results.

The purpose of this introductory search was to establish a baseline of information regarding the symptoms of PAD or concomitant pathologies that were quickly observable in a typical Primary Care Physician's (PCP) office. Articles were included if they had direct mention of PAD and relation to any abnormal, easily observable physical phenomenon that could be observed without special equipment, e.g. discoloration of a body part. Asia and Africa were exclusion terms due to this review's scope of PAD in the United States. This search directly yielded references 5, 6, 9, and 10. Reference 6 provided a link to reference 36, and reference 10 provided reference 8 by way of the aforementioned method of

including relevant sources cited within search results. Reference 36 was only mentioned in the discussion section of this review.

**2. Include:** [peripheral arterial disease]; [critical limb ischemia]; [diabetic foot]; [wound healing]; ulcer; vascular; management; identification; skin; assessment classification.

Exclude: meta; culture; epidemiology; revascularize. 19 results.

This search served the purpose of exploring the differences in wound healing and ulceration in PAD, as well as in more severe cases of Critical Limb Ischemia (CLI). This search provided references 33 and 34. Reference 34, the baseline results from the EURODIALE study, prompted a search for this specific study on google scholar and the subsequent inclusion of reference 35, the 1-year follow-up of EURODIALE in this review. A wealth of microbiological studies involving cultured ulcer tissue, as well as meta-analyses, which were deemed irrelevant to the topic of this review, necessitating "meta" and "culture" as exclusion terms.

**3. Include:** [peripheral arterial disease]; dermatology; skin; examination; risk factor; epidemiology.

Exclude: outcome; Asia; Africa; receptor. 37 results in English.

This final search was meant to narrow in on specific diseases comorbid with PAD, branching into other specialties. A wealth of protein receptor studies irrelevant to the topic of this review necessitated "receptor" as an exclusion term. References 7, 14, 16, 23, 28, and 32 were found directly in this search. References 17-20 were found within reference 16, all discussing the relation between onychosis and psoriasis within the context of PAD. Reference 23 provided information on the link between PAD and psoriasis, citing references 22, 25, 26, and 27 within this review. Reference 25, in turn, provided reference 24, discussing the microbiological evidence of the interplay between PAD and psoriasis. Reference 21 was cited in both references 17 and 18. Reference 15 was cited within reference 14.

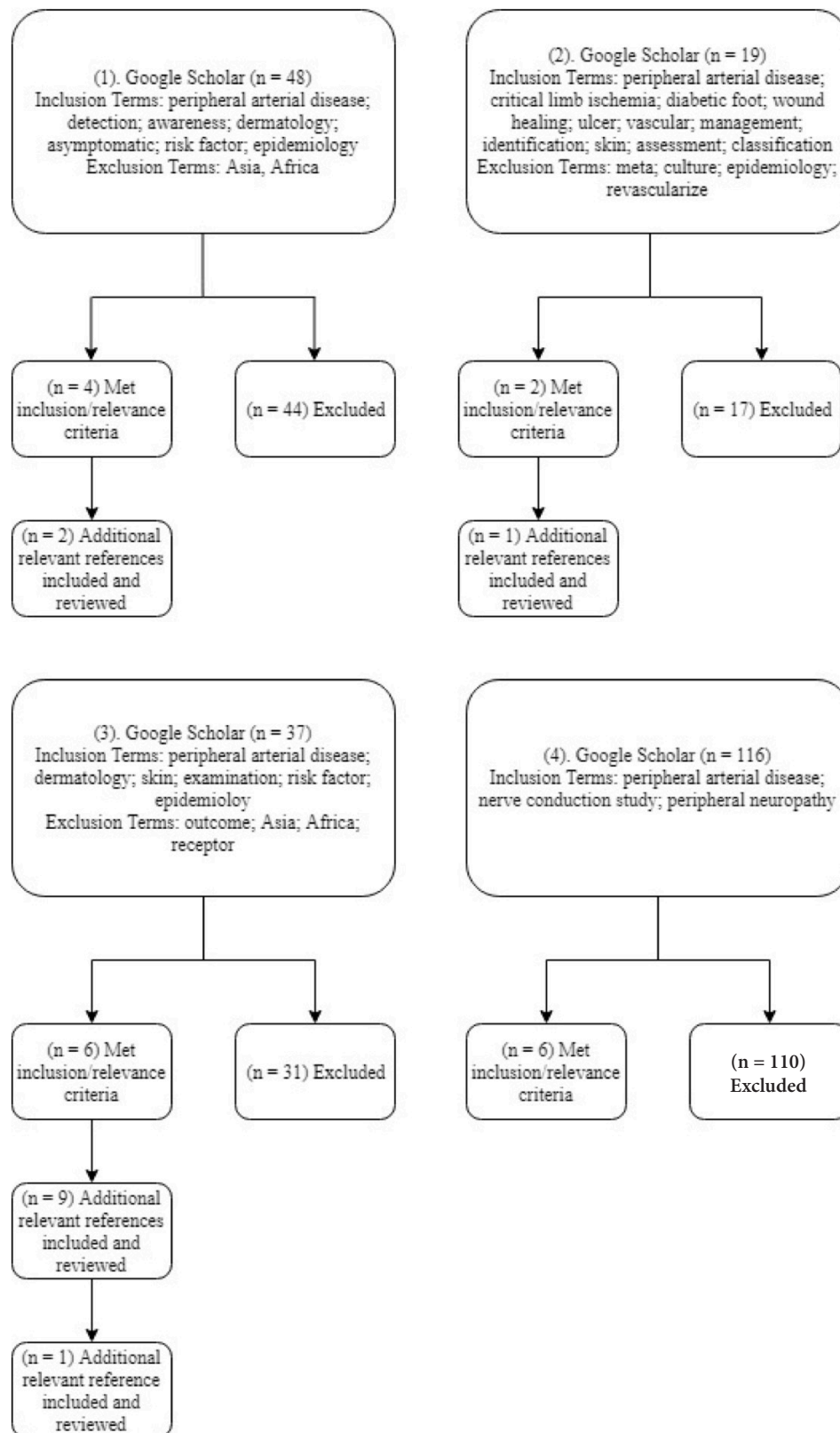
**4. Include:** [peripheral arterial disease]; [nerve conduction study]; [peripheral neuropathy].

116 results in English

After the inclusion of Reference 28, a study on the relationship between PAD and peripheral nerve function, the author interested in exploring the relationship further through the above search protocol. Direct studies were included in this review if they explored the relationship between PAD and peripheral nerve function, particularly if examinable by Nerve Conduction Study (NCS). Studies were excluded if they involved participants in a PAD group that exhibited progressed ischemic symptoms like gangrene or ulceration of the foot. This search protocol produced references 29 – 31, all studies illuminating a significant relationship between PAD and observable abnormalities on NCS.

## RESULTS

A total of 31 sources were retrieved for review and discussion in this literature review using the methods section outlined above.



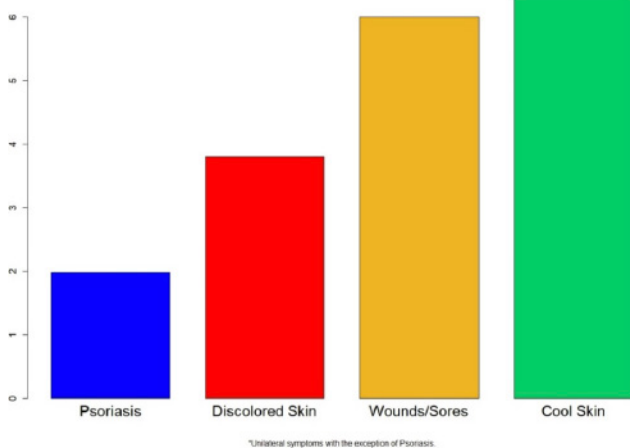
Six sources were included from Search 1, three sources from Search 2, and a total of 16 sources were included from Search 3. Three sources were included from Search 4. The two sources included in this section not obtained through the three outlined search algorithms are the 2016 and 2005 ACC/AHA Guidelines for the Management of Patients With Peripheral Arterial Disease, references 1 and 2, respectively.

## PHYSICAL EXAM

A total of four reviewed papers discussed symptoms discoverable through physical examination requiring no specialized equipment that indicated PAD. Examination of the lower extremities for "absence of hair growth," namely on the toes, "perspiration, dry skin, and cool temperature" are easily identifiable and may indicate subtle changes in physiology as a result of reduced lower-extremity perfusion.<sup>6</sup> Cooler, bluer skin (cyanosis) is one common sign of PAD, though a more severely ischemic foot can appear pink and warm "because of arteriovenous shunting".<sup>7</sup> A large-scale study on 2,455 Netherlandish participants demonstrated significant ORs for predictability of PAD by Ankle-Brachial Index (ABI) < 0.9 from cool skin (OR 6.4), discolored skin (particularly cyanosis, OR 3.8), and wounds or sores on the lower extremity (OR 6.0) (Figure 1).<sup>8</sup> "Calf atrophy, dependent rubor and elevation pallor, loss of hair over the dorsum of the foot, thickening of the toenails, and shiny, scaly skin due to the loss of subcutaneous tissue...are indications of severe tissue ischemia," requiring immediate evaluation and treatment.<sup>9</sup>

FIGURE 1:

OR Comparison of PAD Risk Factor\*



## CLINICAL TECHNIQUES

Four papers in this review discussed palpation techniques performable by all general practitioners with common medical equipment. Mohler III's literature review claims superficial femoral artery (SFA) stenosis, the most common form of PAD, is typically characterized by normal femoral pulse and absent distal pulses. In the Buerger Test, the clinician instructs the patient to lie supine, and slowly elevates the leg evaluating for the development of pallor in the limb (a positive test), and noting the angle of the leg at

which pallor develops. Though this review did not find any studies directly comparing the effectiveness of the Buerger Test to an ABI and predictability of PAD, the Buerger Test can indicate issues with circulation to the leg through determining the dependent angle for circulation, and easily segway into an exam for venous filling time.<sup>6</sup> Capillary refill time after relieving manual pressure to the plantar aspect of the great toe is associated with PAD (LR 1.90), as is venous filling time greater than 20 seconds (LR 3.6) to a vein identified in the Buerger test with the patient now sitting upright with legs hanging down.<sup>10</sup> Absence of unilateral posterior tibial (PT) and dorsalis pedis (DP) pulses predict ABI < 0.9 (LR 3.57), as does auscultation of a femoral bruit (LR 2.90)<sup>11</sup> (Figure 2). The study on Netherlandish patients demonstrated predictability of ABI < 0.9 in patients with normal femoral pulse in one leg and absent in the other (OR 6.1), weak unilateral femoral artery pulse (OR 3.7), and femoral bruit (OR 7.8). Additionally, if one foot lacked both DP and PT pulse or if one of these was absent while the other weakened, this was also found to be a strong, significant predictor for ABI < 0.9 (OR 30.4), as was any unilateral weakened foot pulse (OR 8.6)<sup>8</sup> (Figure 3).

FIGURE 2:

LR Comparison of PAD Detection Methods

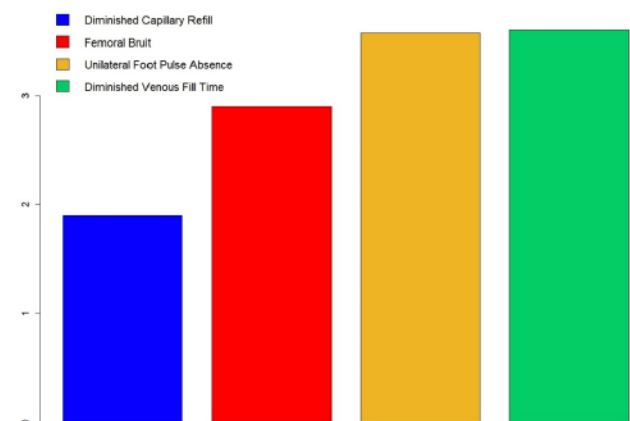
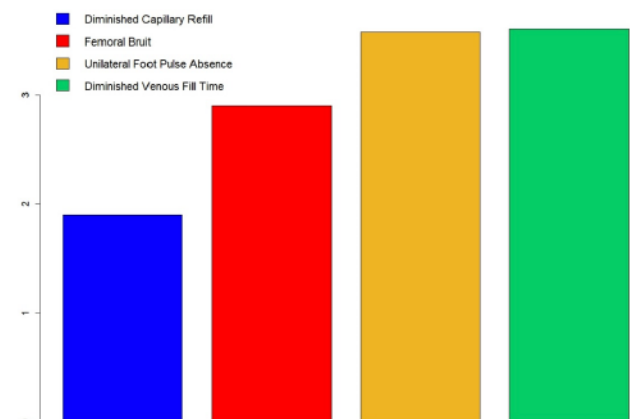


FIGURE 3:

OR Comparison of Pulse Palpation Techniques for PAD Detection



## ONYCHOMYCOSIS

Four sources in this review directly demonstrated an epidemiological relationship between PAD and the fungal toenail infection, onychomycosis. Identified by abnormal toenail growth and confirmed through lab pathology<sup>12</sup>, onychomycosis was shown to affect 35.1% of patients visiting a vascular clinic for PAD, confirmed by ABI < 0.8. In another study, 83.3% of smokers of at least two packs per day suffered from onychomycosis, and PAD remained a predictor of onychomycosis even when adjusting for the effect of smoking (ROR 4.8)<sup>13</sup>. Onychomycosis affected 22% of elderly diabetic patients in another.<sup>14</sup> Patients with diabetes (the other token risk factor for PAD besides age) were three times as likely to suffer from onychomycosis than those without diabetes.<sup>15</sup>

## PSORIASIS/ONYCHOMYCOSIS

Six papers discovered in this review mentioned an epidemiological relationship between onychomycosis and psoriasis. Many studies debate the exact nature of the relationship between onychomycosis and psoriasis, as demonstrated by Szepietowski and Salomon's 2007 literature review.<sup>16</sup> Gupta and colleagues found onychomycosis in 13% of psoriatic patients, and a 27% presence of any fungal nail infection in psoriatic patients with any nail abnormality in 1997.<sup>17</sup> Yeast-like fungi and molds were uncommon. In 2004, Hamnerius and colleagues found no difference in prevalence of onychomycosis in psoriatics vs. non-psoriatics.<sup>18</sup> Larsen and colleagues showed no difference in 2003 in prevalence of onychomycosis in their psoriatic vs non-psoriatic subjects, but they did find a higher percentage of yeast colonization in those suffering the toenail infection in the psoriasis group.<sup>19</sup> Stander and colleagues found a large difference in presence of yeasts in subjects with directly psoriatic nails (23.9%) vs. psoriatics without nail abnormalities (6.1%) in 2001<sup>20</sup>, with similar results in Staberg and colleagues' 1983 study.<sup>21</sup>

## PSORIASIS

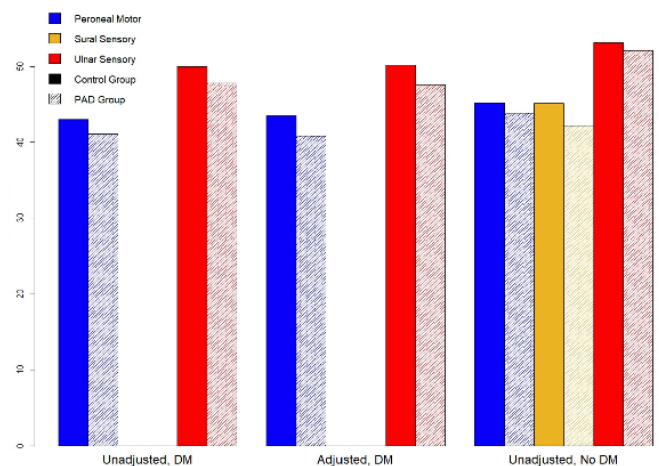
Six additional studies confirmed concomitance between psoriasis and PAD or classic PAD-related risk factors. A major data review of the Miami VA Medical Center Database found that psoriasis carried an OR of 1.98 to PAD, as determined by previously entered ICD-9-CM codes in the database.<sup>22, 23</sup> Early electron microscope studies show "microscopic abnormalities in the cutaneous blood vessels of psoriatic patients,"<sup>24</sup> and suggest a relative risk of 2.6 for PAD if a diagnosis of psoriasis is present.<sup>25</sup> Another study found increased hazard ratios (HR) in psoriatic participants for many PAD risk factors and associated complications: Diabetes (1.33), hypertension (1.09), obesity (1.18), hyperlipidemia (1.17), myocardial infarction (1.21), angina (1.20), atherosclerosis (1.28), peripheral vascular disease (1.29), and stroke (1.12).<sup>26</sup> Another study found that risk of stroke was elevated by 44% in those with "severe psoriasis."<sup>27</sup>

## PERIPHERAL NERVE CONDUCTION STUDIES

Four direct studies were found illuminating a relationship between PAD and peripheral nerve performance. Participants without diabetes demonstrated significantly diminished peroneal motor, sural sensory, and ulnar sensory nerve conduction velocity, amplitude, and onset latency ( $p < 0.05$ ) in unadjusted analyses. The effect persisted in unadjusted analyses of patients with diabetes but only in conduction velocity of the peroneal motor nerve, and velocity and latency of the ulnar sensory nerve. Though diabetes' peripheral neurodegenerative effect may be a confounding variable in the effect of PAD on nerve conduction, this study suggests the possibility of an independent effect of PAD. After adjusting for several confounding variables including but not limited to age, sex, and smoking status, nerve function was still significantly diminished in the peroneal motor and ulnar sensory conduction velocity, and sural sensory impulse amplitude<sup>28</sup> (Figure 4).

FIGURE 4:

Significant Effects of PAD on Nerve Conduction Velocity



In a study on participants aged 60+, individuals determined to have PAD by ABI < 0.9 were found to have slower nerve conduction velocity of the peroneal nerve (44.16 vs. 43.04 m/s,  $p = 0.003$ ), consistent with findings in McDermott et al, 2006.<sup>29</sup> Adding to the evidence of the interplay between diabetes and PAD on peripheral nerve abnormalities, a study on 240 Chinese participants categorized their subjects into three groups: confirmed diabetes (determined by presenting symptoms and abnormalities on NCS), subclinical diabetes (symptoms consistent with diabetic peripheral neuropathy, but no abnormal findings on NCS), and those without diabetic peripheral neuropathy (control). The study found significantly higher prevalence of PAD as determined by ABI < 0.9 in their confirmed group than either the subclinical or control group (30%, 7.7%, and 3.4%, respectively).<sup>30</sup> Finally, a study recruited patients in Greece and determined early-stage PAD through clinical decisions based on patient history and physical exam. Lack of ABI in the determination of PAD may detract from the study's validity. In any case, a dynamic F-wave study, a specialized test that can be added to a routine NCS, demonstrated to the experimenters that



participants with PAD experienced significantly greater F-wave duration in the tibial motor nerve than pre-exercise (average  $16.3 \pm 3.5$  vs.  $13.9 \pm 2.9$ ,  $p = 0.017$ ). The non-PAD control group experienced no difference pre and post-exercise.<sup>31</sup>

## FOOT ULCERATION

Five papers in this review discussed the characteristics of ulcers that specifically result from or relate to PAD. PAD specifically causes arterial ulcers<sup>32</sup>, appearing “punched out,” with a deep, necrotic wound bed typically on the lateral malleolus, tibial region, or other pressure points. Unrelated venous ulcers are shallower, containing “granulation tissue or yellow fibrin,” and are commonly between the lower calf and medial malleolus.<sup>7</sup> Arterial ulcers, particularly in patients with severely diminished ABIs, do not heal properly without revascularization.<sup>33</sup> The Eurodiale study on diabetic foot ulcers examined the relationship between PAD and wound-healing, finding PAD by ABI  $< 0.9$  in 49% of participants presenting with diabetic foot ulcers, and were more likely to have infection in their ulcer than non-PAD participants (63% vs. 53%,  $p < 0.05$ ).<sup>34</sup> The one-year follow-up of this study found that 23% of participants had still not yet healed, PAD being an independent predictor of non-healing with OR 2.<sup>31,35</sup>

## DISCUSSION

Despite the rising incidence of PAD, physician awareness can be improved; an Illinois survey of internists presented with a hypothetical case of an obese 65-year-old male with hypertension, showed that only 37% responded that they would attempt to obtain a history concerning PAD.<sup>36</sup> Furthermore, the US PARTNERS Program study including data on 6,417 diabetic smokers between ages 50 and 69 determined that of the 29% of participants with PAD, 55% received their diagnosis only from the ABI administered at screening.<sup>9</sup>

Claudication is the classic finding in symptomatic PAD, however, this can be masked by patient changes in lifestyle. A detailed history and physical exam may be able to determine patient changes in physical activity due to asymptomatic PAD alerting the physician to PAD workup. This review illuminates certain clinically observable symptoms, including examinable skin abnormalities, findings in clinical techniques, onychomycosis, psoriasis, and NCS findings that may be used as a clue to underlying PAD.

Asymptomatic diagnosis can be made by positive ABI, a clinical measure of systolic pressure at the ankle to systolic pressure at the arm obtained with a pressure cuff.<sup>1,2</sup> Having been demonstrated to be over 90% specific and sensitive,<sup>37,38</sup> it is explicitly recommended by the American College of Cardiology and American Heart Association for accurate PAD diagnosis.<sup>1,2</sup>

The under-diagnosis of asymptomatic PAD is an issue in United States healthcare. End stage PAD will progress to Critical Limb Ischemia (CLI) and 20% of patients diagnosed with CLI die within 1 year, while another 20% suffer a lower-extremity amputation (LEA) within one year. Of all patients with PAD presenting with claudication, 5% progress within five years to receive LEA.<sup>39</sup> Roughly

15% of PAD patients at any stage presenting with non-healing diabetic foot ulcers undergo a major LEA within one year, of which 15% die within one year and nearly 50% within 5 years.<sup>40</sup> PAD can also result in complications like stroke, myocardial infarction, and angina, but at its core, a PAD diagnosis is associated with a five-year death rate of 33.2%.<sup>41</sup>

This systematic review was conducted in order to increase awareness of less-common pathologies or physically observable symptoms comorbid with asymptomatic PAD in primary care. Increased awareness can lead to early diagnosis, which may improve patient outcome.

## CONCLUSION

There are several predictive findings of PAD that can be identified in the primary care setting, including dermatological abnormalities, positive findings on several clinical techniques, and presence of psoriasis, onychomycosis, or NCS abnormalities. Early diagnosis of PAD may lead to improved patient outcomes. PCPs are functionally patients' first line of defense within the bounds of medical practice against disease. Given the growing incidence and prevalence of PAD in the US population, difficulty in diagnosing asymptomatic disease until late stages, as well as the dire late-stage prognosis of PAD, it is paramount that PCPs be aware of the disease's scope, and take the extra time in their practice to palpate for lower-extremity pulses, auscultate bruits, perform a thorough physical exam, and ask relevant clinical questions in the patient interview so that signs of asymptomatic disease can be detected earlier. Such steps may be key in the preventing complications, particularly in at-risk populations such as the elderly, diabetics, and smokers. These practices, if put into place regularly, may lead to earlier-stage diagnosis, subsequent treatment, and finally improved prognoses in PAD.

## AUTHOR DISCLOSURES:

No relevant financial affiliations

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