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Original article

PREVENTING PERIPHERAL ARTERIAL DISEASE: THE CRUCIAL ROLE OF CARDIOLOGISTS.

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ABSTRACT

Peripheral artery disease (PAD) is a clinical appearance of systemic atherosclerotic disease. Individuals diagnosed with PAD exhibit an unfavorable prognosis characterized by an elevated susceptibility to cardiovascular (CV) occurrences, such as stroke, myocardial infarction, limb ischemia, and cardiovascular mortality. Consequently, the timely identification and management of PAD assume paramount significance. PAD and CAD (coronary artery disease) exhibit a shared pathogenesis and risk elements, thereby conferring upon cardiologists a distinct advantage in the screening, diagnosis, and management of PAD. Furthermore, PAD and CAD exhibit overlapping treatment objectives, which encompass a proactive alteration of risk elements to mitigate the likelihood of cardiovascular events. PAD continues to be a condition that is frequently overlooked in terms of diagnosis and treatment, resulting in potential legal ramifications within the medical field. The objective of this review is to raise alertness among clinicians concerning the importance of PAD, as the responsibilities of cardiologists continue to broaden. Recognizing the systemic nature of PAD and its association with adverse cardiovascular outcomes underscores the importance of early diagnosis and proactive management. Future research, interdisciplinary collaboration, and policy development should all aim to improve the identification and care of individuals with PAD, ultimately reducing the burden of cardiovascular events and enhancing patient care.

Keywords: *Atherosclerosis; Peripheral Artery Disease; Prevention; Cardiologist*
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Introduction

Atherosclerosis is a complex, chronic inflammatory vascular disorder that frequently impacts one or multiple vascular regions within an individual [1]. Peripheral arterial disease (PAD) is a comprehensive field of clinical manifestations that possess the capacity to affect multiple vascular territories, including the upper and lower extremities, as well as the carotid, vertebral, mesenteric, and renal arteries. The main emphasis of this review pertains to atherosclerosis, with a specific focus on its manifestation in the lower extremities. Patients diagnosed with PAD demonstrate a markedly increased vulnerability to mortality from all causes and cardiovascular events. Furthermore, it is imperative to note that these individuals are confronted with an elevated susceptibility to encountering stroke or myocardial infarction (MI), a risk that is at the very least correspondent to the observed risk in people who have received a diagnosis of coronary artery disease [2]. Due to the extensive prevalence of atherosclerotic arterial disease in various anatomical locations, cardiologists possess a notable advantage in their proficiency in performing screening, diagnosis, and therapeutic interventions for PAD. The following analysis explores the occurrence and examination of multisite arterial disease and the current medical interventions designed to improve results in individuals suffering from lower extremity peripheral arterial disease (LE-PAD).

Methodology

Literature Review

A comprehensive literature search was conducted to identify relevant studies and publications related to peripheral arterial disease (PAD), with a specific focus on its manifestation in the lower extremities (LE-PAD). Databases such as PubMed, MEDLINE, and relevant cardiology journals were systematically searched using keywords and medical subject headings (MeSH) related to PAD, atherosclerosis, and cardiovascular outcomes.

Data Collection

Data about the pathophysiology, epidemiology, diagnosis, and treatment of LE-PAD were extracted from identified studies, clinical trials, guidelines, and expert consensus statements. The inclusion criteria for selecting studies included relevance to LE-PAD, publication in peer-reviewed journals, and availability of data on cardiovascular outcomes associated with LE-PAD.

Data Analysis

Data obtained from the selected studies were analyzed to provide insights into the epidemiology and prognosis of LE-PAD, its association with coronary artery disease (CAD) and carotid occlusive disease (COD), as well as its impact on clinical outcomes such as cardiovascular events and mortality.

Pathophysiology Background

LE-PAD is a medical condition characterized by the presence of arterial blockages in the lower extremities. These blockages outcome in a decline in blood flow to the affected areas, leading to various clinical manifestations. These manifestations can range from intermittent claudication, which is pain or discomfort during physical activity, to critical limb ischemia (CLI), a severe condition categorized by inadequate blood supply to the affected limb. Atherosclerosis, a prevalent pathological condition, is distinguished by the accumulation of lipids within the intimal layer of arterial walls, followed by consequent inflammation. This disease process stands as the foremost prevalent etiology. Arteriosclerosis, categorized by the rigidity and thickening of the arterial wall accompanied by degenerative alterations in the extracellular matrix of the media layer, frequently occurs concomitantly with atherosclerosis and serves as an autonomous prognosticator of morbidity and mortality across all causes [3].

The presence of modifiable risk variables has been observed in association with atherosclerotic CAD and Carotid Occlusive Disease (COD), which have also been found to contribute to the development of atherosclerosis in the arteries of the lower limbs. Cigarette smoking and diabetes mellitus have been recognized as the most prominently correlated risk variables for LE-PAD. Additionally, other factors that lead to the development of LE-PAD include hypertension, obesity, dyslipidemia, inflammation, and chronic kidney disease, as indicated by the conc. of C-reactive protein. In contradistinction, arterial stiffening is intricately associated with advancing age and elevated BP. Infrequently, LE-PAD may arise as a consequence of embolism, thrombosis, vasculitis, entrapment, or fibromuscular dysplasia.

Epidemiology and Prognosis

CAD in Patients with LE-PAD

Peripheral artery disease, with a global prevalence of more than 200 million individuals [4], is considered the 3rd most common manifestation of atherosclerotic cardiovascular disease, following CAD and stroke. In the year 2019, it was estimated that a total of 29.5 million individuals residing in 57 European countries were affected by LE-PAD, which is clinically defined as the occurrence of stenosis or occlusion in the arteries of the lower limbs. Its prevalence increases notably with age, e.g., approximately 8% in those aged 60-64 and around 25% in those aged 90 or older [5].

The iliofemoral region is often most affected in middle-aged asymptomatic individuals, indicating a 70% likelihood of disease elsewhere. On the contrary, the lack of it indicates a 67% likelihood of being free from disease in additional vascular regions [6]. The presence of atherosclerotic disease concurrently affecting a minimum of two significant vascular territories is referred to as "multisite" artery disease.

LE-PAD individuals face higher susceptibility to subclinical coronary and cerebrovascular conditions, increasing their cardiovascular event risk. Angiographically significant CAD is present in 25% to 70% of LE-PAD individuals, with two-thirds having concurrent CAD or cerebrovascular disease according to the REACH registry [7].

LE-PAD in Patients with CAD

CAD, a prevalent cardiovascular disorder and a prominent contributor to global mortality exhibits notable parallels with LE-PAD in its age-related prevalence. In individuals aged 40 and above, the male population is confronted with a lifetime risk of 49%, whereas the female population bears a risk of 32% [8]. The impact of LE-PAD on the prognosis of patients with CAD is observed, thereby influencing the treatment decisions made by the heart team for individuals with left-main or three-vessel CAD. These decisions are based on the utilization of the Syntax Score II, a predictive tool that assesses the risk of mortality. In people diagnosed with MI, the occurrence of concomitant peripheral artery disease is related to a significantly elevated risk of experiencing adverse events. A comprehensive examination of a cohort comprising 2 million patients diagnosed with MI revealed that approximately 50% of these individuals exhibited pre-existing PAD. The analysis further demonstrated a positive correlation between the quantity of affected vascular beds and unfavorable outcomes, specifically highlighting the heightened vulnerability of patients with LE-PAD [9]. Furthermore, within a comprehensive investigation involving a vast cohort of 1.4 million individuals who underwent the medical procedure known as percutaneous coronary intervention (PCI), the prevalence of PAD was determined to be 14%. Individuals diagnosed with PAD exhibited a statistically significant elevation of 22% in the likelihood of experiencing mortality from any cause when compared to their counterparts without this condition. The LE-PAD intervention exhibited the most notable influence on mortality, with cerebrovascular disease ranking second in terms of impact. In the context of MI, the odds of in-hospital mortality were found to increase in correlation with the extent of vascular involvement [10]. Early suspicion and detection play a pivotal role in light of the intimate association between CAD and PAD.

COD in Patients with LE-PAD

Carotid occlusive disease (COD) typically involves atherosclerosis in the extracranial internal carotid artery. It is more prevalent in males and significantly increases with age. In the male population, the prevalence of moderate carotid artery stenosis (defined as a narrowing of ≥ 50%) varies from 0% - 7.5% across different age groups. Similarly, the occurrence of severe stenosis varies from 0.1%-3.1% [11].

Stroke, a major cerebrovascular condition, is the 2nd major cause of both disability and mortality worldwide. It contributes to around 10-20% of ischemic strokes [12]. Importantly, COD is commonly found in individuals with LE-PAD due to shared underlying causes. The incidence of significant coronary artery disease (≥ 50% stenosis) is notably higher in people with more severe LE-PAD, especially in those with ABIs below 0.5 and those classified as Fontaine Stage IV. These factors, identified in a previous study [13], independently increase the likelihood of substantial coronary artery disease.

LE-PAD in Patients with COD

There is a paucity of data about the occurrence of LE-PAD in individuals diagnosed with CAD. According to the prevailing guidelines established by the ESC, the occurrence of LE-PAD in individuals with severe COD falls within the range of 18% to 22% [14]. Numerous investigations have consistently demonstrated a substantial occurrence of LE-PAD among individuals who have experienced cerebrovascular events. Furthermore, it has been established that the severity of LE-PAD is associated with an elevated susceptibility to recurrent cerebrovascular events. In the OECROSS study, which focused on individuals with ischemic stroke or transient ischemic attack (TIA), the occurrence of LE-PAD was found to be 45% [15].

Diagnosis

Multisite arterial disease invariably results in adverse clinical outcomes. Nevertheless, the efficacy of examination for asymptomatic disease in alternative anatomical locations to enhance prognosis remains inconclusive. The AMERICA study aimed to assess the comparative effectiveness of a proactive intervention strategy, involving the identification and management of asymptomatic extra-coronary atherothrombotic disease, in comparison to the conventional approach for treating coronary atherosclerosis. The proactive strategy involved the implementation of aggressive secondary prevention measures and/or revascularization procedures. The conventional methodology entailed the utilization of clinically guided multisite artery diagnosis and standard pharmacological intervention. Following a comprehensive two-year follow-up period, it has been determined that the implementation of the proactive strategy did not yield a significant decrease in cardiovascular events when compared to the conventional strategy. Significantly, it is worth mentioning that both cohorts were provided with equally comprehensive secondary prevention measures, thereby mitigating the potential impact of the proactive strategy. Henceforth, by the guidelines set forth by the ESC, it is imperative to conduct a thorough assessment of symptoms and indications of PAD, encompassing the possibility of concomitant afflictions in other anatomical regions, as well as CAD. Additional diagnostic tests may be necessary when clinical suspicion arises [14].

Diagnosis of LE-PAD:

During cardiology visits, focus on LE-PAD symptoms, including intermittent claudication or rest pain. Examine peripheral pulses, inspect extremities, and listen for arterial bruits. Use Fontaine and Rutherford classifications for LE-PAD. ABI, the ratio of the ankle to brachial systolic blood pressure, is a simple diagnostic tool. Normal ABI is 1.00 to 1.40, ≤ 0.90 is abnormal, and 0.91 to 0.99 is borderline. ABI ≤ 0.90 has 83%-99% specificity and 69%-73% sensitivity for > 50% stenosis. Leg claudication patients often have ABI 0.5-0.8, while CLI patients have ABI < 0.5. In diabetes or renal insufficiency, ABI can be negatively high due to artery calcification, so toe brachial index (TBI) is an alternative with TBI < 0.7 considered abnormal. ABI is also used for hypertension-mediated organ damage (HMOD) screening, though other markers like carotid-femoral pulse wave velocity are more common in HMOD (40-60%) than low ABI (<5%). Pulse wave velocity (PWV) measures arterial stiffness, inversely related to compliance, and femoral-ankle PWV (faPWV) assesses lower limb arterial stiffness, both associated with cardiovascular disease [16]. MRA and CTA are imaging modalities that offer superior resolution; however, it is important to note that they entail exposure to ionizing radiation and the administration of contrast agents. Angiography is widely regarded as the definitive diagnostic modality for patients requiring revascularization procedures. The guidelines established by the ESC advocate for the screening of LE-PAD using clinical examination and/or ABI in individuals who meet the following criteria: age greater than 65, high cardiovascular risk, presence of atherosclerosis in other regions of the body, and those who are scheduled to undergo coronary artery bypass grafting (CABG) with saphenous vein harvesting [14].

Coronary Artery Disease (CAD) Diagnosis:

In light of the frequently observed comorbidity of PAD and CAD, it is imperative to explore the manifestation of CAD symptoms, including angina or anginal equivalents, in individuals with LE-PAD. The initial step involves obtaining a resting 12-lead ECG, a commonly employed diagnostic tool. This procedure frequently reveals nonspecific alterations in the ST-T wave complex or the presence of abnormal Q waves. Conduct a resting

transthoracic echocardiogram to exclude alternative etiologies, detect wall motion abnormalities associated with CAD, evaluate left ventricular ejection fraction (LVEF), and assess diastolic function. The diagnostic approach for obstructive CAD involves the utilization of various tests, depending on the pre-test probability. These tests evaluate the functional aspects of the heart and its stress response, helping to identify any potential obstructions in the coronary arteries. On the other hand, anatomical tests involve the use of coronary CT angiography or invasive angiography. These tests provide a detailed assessment of the anatomical structures of the coronary arteries, allowing for the visualization of any potential blockages or narrowing. The selection of the appropriate test depends on the pre-test probability, which considers various factors such as the patient's clinical presentation, risk variables, and symptoms. By employing the most suitable diagnostic test, healthcare professionals can accurately diagnose obstructive CAD and guide the subsequent management and treatment strategies [17]. The guidelines established by the ESC advocate for the utilization of ECG screening in people with LE-PAD [14].

Carotid Occlusive Disease (COD) Diagnosis:

During cardiology visits, listen for carotid bruits to detect COD. Noninvasive imaging methods for COD include duplex ultrasound, MRA, and CTA, with duplex ultrasound as the initial choice. Intra-arterial digital subtraction angiography is rarely needed. ESC guidelines do not provide specific recommendations for COD screening in LE-PAD patients [14].

Treatment

Atherosclerosis is the main cause of PAD, sharing modifiable risk variables with CAD. The primary goal in managing LE-PAD is to decrease cardiovascular morbidity and death rate, alleviate claudication symptoms, eliminate rest pain, and preserve limb viability. This involves lifestyle changes and pharmacological interventions.

Lifestyle Modifications:

Promote the adoption of a health-conscious lifestyle, encompassing the consumption of a well-balanced diet, effective weight control, consistent engagement in physical activity, and the cessation of tobacco use. The Mediterranean diet has been shown to decrease the risk of PAD. The implementation of low to moderate-intensity aerobic exercise has been shown to reduce the incidence of cardiovascular mortality and mitigate the risk of developing cardiovascular diseases. Supervised exercise therapy is efficacious in the management of claudication. The cessation of smoking is of paramount importance, with counseling and pharmacological interventions serving as valuable tools to facilitate successful cessation.

Management of Diabetes Mellitus (DM):

DM is a strong predictor of PAD and increases mortality and amputation risk. Proactive DM management reduces microangiopathic events. Sodium-glucose cotransporter inhibitors (SGLT-2is) like empagliflozin and dapagliflozin benefit PAD patients with DM. Glucagon-like peptide 1 receptor agonists (GLP-1RAs) like liraglutide reduce amputations in type 2 diabetes and high CV risk. ESC guidelines recommend SGLT-2is and GLP-1RAs in PAD patients with DM and CV disease or high CV risk.

Management of Hypertension:

Hypertension, also known as high blood pressure, is a prevalent risk variable for PAD. Diuretic agents, calcium channel antagonists, beta-adrenergic blocking agents, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs) are pharmacological interventions commonly employed in the management of hypertension. ACEIs and ARBs are considered the preferred pharmacological agents for the management of PAD owing to their demonstrated effectiveness in reducing CV events.

Pharmacotherapy for Dyslipidemia:

Dyslipidemia plays a vital role in atherosclerosis. PAD patients are considered to have very high cardiovascular risk. Statins are the primary treatment, reducing MACEs and MALEs. Ezetimibe and PCSK9 inhibitors like evolocumab and alirocumab further lower CV risks in PAD. Inclisiran and bempedoic acid's impact on PAD requires further study.

Antithrombotic Therapy:

Antiplatelet therapy is essential in PAD management, with recommendations varying based on symptoms, revascularization history, and type. Symptomatic intermittent claudication without prior revascularization benefits from single antiplatelet therapy, preferably clopidogrel. DAPT (aspirin and clopidogrel) benefits after endovascular revascularization. Open revascularization calls for single antiplatelet therapy. In high-risk cases, consider anticoagulation with vitamin K antagonists.

Discussion

LE-PAD is a global health concern affecting over 200 million individuals [4]. There exists a robust correlation between the aforementioned condition and a heightened susceptibility to MACEs and MALEs, primarily attributable to its connection with coronary and cerebral atherosclerosis [2]. Management strategies include lifestyle modifications and pharmacological therapy to reduce these risks [14]. However, LE-PAD is often underdiagnosed and undertreated.

For example, a Greek study in 14 primary-care health centers found a 13% prevalence of LE-PAD, with most cases being asymptomatic (11.7%), and only 8.77% of diagnosed patients were aware of their condition [18]. A retrospective analysis was conducted on a cohort of 15891 patients diagnosed with LE-PAD who had undergone peripheral vascular intervention. The study revealed that a significant proportion, approximately 50%, of these patients were not being administered guideline-directed medical therapy (GDMT) as recommended by established clinical guidelines. Individuals who did not receive GDMT exhibited a markedly elevated susceptibility to mortality and amputation, as indicated by previous research [19].

These findings emphasize the importance of integrating ankle-brachial index (ABI) measurement into routine clinical practice to facilitate early LE-PAD detection and the need for increased awareness of optimal medical interventions.

Conclusions

Peripheral artery disease is a pathological condition characterized by the narrowing or occlusion of peripheral arteries, primarily due to the development and progression of atherosclerosis. Given the shared etiology, PAD and CHD often coexist, thereby affording cardiologists a distinct opportunity to conduct screening, establish diagnoses, and administer treatment for LE-PAD. The implementation of an assertive risk modification strategy aimed at mitigating the likelihood of CV events serves as the fundamental approach for managing both conditions. Despite the existence of various therapeutic modalities and specific clinical protocols, individuals afflicted with peripheral artery disease frequently experience suboptimal management.

Limitations

The LE-PAD review depends mainly on literature and observational studies. The lack of current clinical trials or large-scale prospective studies may hinder analysis. The included studies had various patient demographics, diagnostic criteria, and treatment techniques, which may affect interpretation. This heterogeneity may limit results' generalizability.

Recommendations

To improve LE-PAD understanding and management, increase large-scale clinical trials for diagnosis and treatment, assess new medications, promote healthcare professional awareness, emphasize early detection in medical education, foster collaboration among practitioners, engage patients in decision-making, integrate LE-PAD into cardiovascular risk guidelines, and garner policy support for early diagnosis and evidence-based therapies.

List of abbreviations

PAD: Peripheral Artery Disease
CV: Cardiovascular
CAD: Coronary Artery disease
MI: Myocardial Infarction
LE-PAD: Lower Extremity Peripheral Arterial Disease
CLI: Critical Limb Ischemia
COD: Carotid Occlusive Disease
BP: Blood pressure
PCI: Percutaneous Coronary Intervention
ABI: Ankle-Brachial Index
HMOD: Hypertension-Mediated Organ Damage
TBI: Toe Brachial Index
PWV: Pulse Wave Velocity
faPWV: Femoral-Ankle PWV
CABG: Coronary Artery Bypass Grafting
LVEF: Left Ventricular Ejection Fraction
SGLT-2is: Sodium-Glucose Cotransporter Inhibitors
GLP-1RAs: Glucagon-Like Peptide 1 Receptor Agonists
DM: Diabetes Mellitus
ACEIs: Angiotensin-Converting Enzyme Inhibitors
ARBs: Angiotensin Receptor Blockers
GDMT: Guideline-Directed Medical Therapy

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Nil

Conflict of interest

The authors report no conflicts of interest in this work.

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