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Update on peripheral artery disease: Epidemiology and evidence-based facts

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1. Definition

Peripheral artery disease (PAD) is a progressive disorder characterized by stenosis and/or occlusion of large and medium-sized arteries, other than those that supply the heart (coronary artery disease, CAD) or the brain (cerebrovascular disease). PAD affects the lower extremities more commonly than the upper extremity vessels, and may lead to an recurrent fatigue, cramping sensation, or pain that is known as *claudicatio intermittens* (intermittent claudication), which is the most recognized symptomatic subset of lower extremity PAD.

2. PAD epidemiology

It is estimated that >200 million people have PAD worldwide, with a spectrum of symptoms from none to severe. Relatively uncommon among younger people, the prevalence of PAD rises with age and affects a substantial proportion of the elderly population (>20% in >80-year-old individuals). The rate for African-Americans is about twice that of non-Hispanic whites at any given age (Table 1).

PAD is associated with reduced functional capacity and increased risk for cardiovascular morbidity and mortality. Notwithstanding its widespread prevalence, its associations with mortality and morbidity, and the reduced quality of life, PAD remains overall underdiagnosed and undertreated [1–3].

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Conflict of interest

The authors declared that they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Examining the population enrolled in the PARTNERS (Peripheral Arterial Disease Awareness Risk and Treatment: New Resources for Survival) program [4], several important aspects related to PAD epidemiology emerge. PAD is poorly recognized: 44% of cases were diagnosed only after the enrollment, only 49% of the primary physicians treating patients with a prior diagnosis of PAD were actually aware of it, despite documentation in medical records. PAD is very common (prevalence: 29%) in high-risk individuals (>70 years without additional risk factors, or 50–69 years with a history of cigarette smoking or diabetes). Moreover, PAD patients are generally less intensively managed compared with CAD patients [3].

Atherosclerotic cardiovascular disorders represent the leading cause of morbidity and mortality for individuals with diabetes and are the largest contributor to the direct and indirect costs of diabetes. Therefore, cardiovascular risk factors, including hypertension, dyslipidemia, smoking, a family history of premature CAD, chronic kidney disease, albuminuria, should be systematically assessed at least annually in all diabetic patients [1].

3. Are diabetic patients without heart disease at higher risk of developing peripheral vascular disease?

As mentioned above, diabetes mellitus is a known risk factor for cardiovascular disease. Most likely due to neuropathy, patients with both diabetes and PAD have worse lower extremity function than individuals with PAD alone. Furthermore, individuals with both diabetes and PAD are at higher risk than PAD patients without diabetes for a rapid progression of their PAD and for developing CAD. However, whether diabetes alone, in absence of CAD, should be considered a risk factor for PAD, remains controversial. This aspect has been examined in the paper published by Wilcox, New-man and colleagues in this issue of *Atherosclerosis* [5]. Using a large database of more than 3.5 million self-referred participants (40–90 years old), the Authors show that diabetes, when accompanied by cardiovascular risk factors (including hypertension, hyperlipidemia, obesity, and cigarette smoking), confers a three-fold increased odds of PAD and carotid artery stenosis, even in absence of CAD. Current smoking was associated with the highest odds of PAD. These researchers had previously demonstrated that CAD and diabetes synergistically increase the odds of PAD [6]: indeed, individuals with both diabetes and CAD have odds of developing PAD greater than the product of their individual odd ratios.

Notably, the rates of CAD in patients with diabetes appear to depend in part on coexisting risk factors: patients with diabetes and two or fewer risk factors had minimally increased odds of developing PAD compared with non-diabetic patients with CAD [5], suggesting that diabetes alone – which represents a relatively uncommon condition in the clinical scenario – is not an independent risk factor for PAD.

4. Is diabetes a coronary risk equivalent?

In trials of acute coronary syndromes, diabetic patients have shown an increased risk for subsequent cardiovascular events. Therefore, experts have argued that diabetic patients without coronary events should be treated in a similar fashion to their counterparts with

CAD. Since the National Cholesterol Education Program Adult Treatment Panel (ATP) III guidelines (2002), diabetes mellitus has been considered a coronary risk equivalent (*i.e.* an individual having a 10-year risk of developing CAD >20%). This determination was supported by evidence that CAD event rates in diabetic individuals without known CAD were as high as those in non-diabetic individuals with prior CAD. A seminal observational study performed in a Finnish population cohort, demonstrated that diabetic patients have a risk for future major coronary events similar to that of patients with previous myocardial infarction, suggesting that diabetic patients should be treated as if they had existing CAD [7]. This study had some weaknesses, such as the lack of power to detect differences between two groups of patients; moreover, patients were self-selected rather than derived from a population-based cohort. Nevertheless, primary prevention efforts to reduce coronary CAD risk in diabetic patients were greatly intensified following this report.

Studies performed in other population groups, however, have provided contradictory results, with some reports supporting the concept of CAD risk equivalent and others not. A 2009 meta-analysis examining 13 studies (for a total of 19,072 diabetic patients) did not support the hypothesis that diabetes is a coronary risk equivalent, showing that patients with diabetes alone had a 43% lower risk of developing CAD than non-diabetic individuals with prior CAD [8]. However, this meta-analysis did not include the results obtained in a large Danish study (population study of 3.3 million people; age>30) published in 2008, demonstrating that diabetic patients requiring glucose-lowering therapy and non-diabetics with a prior myocardial infarction carry the same cardiovascular risk [9].

Diabetes mellitus is a complex disease that encompasses multiple disturbances of glucose homeostasis, and the severity of the disease and its duration have to be considered when assessing the cardiovascular risk [10]. Indeed, a prospective study of men aged 60–79 years followed up for a mean of 9 years indicated that the threshold for disease duration to be regarded as risk equivalency is ~8 years: only patients with longer duration of diabetes (≥8 years) showed a significantly increased CAD risk [11]. These results were confirmed in a large, ethnically diverse, real-world population (1,586,061 individuals; age range: 30–90 years) showing that the risk of future CAD over a 10-year follow up for patients with a history of either diabetes or CAD was similar only among those with diabetes of long duration [12]. Instead, compared to individuals without a history of diabetes or CAD, prevalent diabetes was associated with approximately double, and prior CAD was associated with triple the coronary risk, respectively.

A recent meta-analysis evaluating the role of diabetes in PAD has shown that diabetes, independently from other major vascular risk factors, substantially increases vascular risk in both men and women [2]. However, lifestyle changes to reduce smoking and obesity and use of cost-effective drugs that target major vascular risks (including statins and antihypertensive drugs) – while remaining important in both men and women with diabetes – might not reduce the relative excess risk of occlusive vascular disease in women with diabetes [2]. Hence, in such a controversial field, gender-related differences could play a fundamental role [13].

5. Diagnosis and treatment: translating scientific evidence into clinical practice

The diagnosis of lower-extremity PAD is established by the resting ankle-brachial index (ABI), calculated as the ratio of systolic blood pressure in the ankle and the higher of the two brachial artery pressures. ABI can be assessed with or without segmental pressures and waveforms; leg segmental pressure measurements can be used to establish a diagnosis when anatomical localization is required to design a therapeutic plan. Resting ABI results should be reported as: abnormal (≤0.90), borderline (0.91–0.99), normal (1.00–1.40), or non-compressible (>1.40).

The toe-brachial index (TBI) should be used to establish a diagnosis in subjects in whom lower extremity PAD is clinically suspected but the ABI is not reliable (*e.g.* ABI>1.40 due to non-compressible vessels) [14]. Patients with exertional non–joint-related leg symptoms and normal or borderline resting ABI (0.91–1.40) should undergo exercise treadmill ABI testing, valuable for differentiating arterial claudication from non-arterial causes of pain, to evaluate the magnitude of the functional limitation of claudication, and/or to assess the response to therapy.

Imaging: duplex ultrasound, computed tomography, or magnetic resonance is useful to diagnose anatomic location and severity of stenosis for patients with symptomatic PAD in whom revascularization is considered, whereas invasive angiography is useful for patients with critical limb ischemia (CLI) in whom revascularization is considered; CLI is defined as chronic (≥2 weeks) ischemic rest pain, non-healing wound/ulcers, or gangrene in 1 or both legs attributable to objectively proven arterial occlusive disease.

Since ~65% of deaths in diabetic patients are from cardiovascular causes, the management of diabetes has recently shifted from a glucocentric approach to an aggressive multifactorial strategy to identify and target cardiovascular risk factors. Therapeutic options aimed at reducing adverse cardiovascular event rates associated with PAD include promotion of daily exercise, adoption of a non-atherogenic diet, modification or elimination of atherosclerotic risk factors, including hypertension, smoking, dyslipidemia, and diabetes. Pharmacotherapy is required when target levels of blood pressure, plasma glucose, and LDL cholesterol (<100 mg/dl, <70 mg/dl in very-high-risk patients) are not reached.

Antiaggregant therapy (aspirin 75–162 mg/day or clopidogrel 75 mg/day) is recommended as secondary prevention strategy in patients with diabetes and a history of atherosclerotic cardiovascular disease and may be considered as primary prevention strategy in individuals with type 1 or type 2 diabetes who are at increased cardiovascular risk (this category includes most diabetic women and men aged ≥50 years with at least one additional major risk factor and not at increased risk of bleeding) [1,3].

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Table 1

Peripheral artery disease (PAD) and evidence-based medicine.

PAD: 10 EVIDENCE-BASED FACTS
• The risk of PAD increases substantially with age [15]
• >50% of PAD patients are asymptomatic [14]
• The presence of PAD is associated with a 2-fold increase in the prevalence of heart failure [16]
• 20–30% of individuals with PAD have diabetes mellitus [17]
• Diabetic patients have 2–4 times the risk of developing PAD, CAD, and ischemic stroke [8]
• Smokers have 2.5 times the risk of developing PAD [3]
• Atherosclerosis accounts for more than 90% of cases of PAD [14,18]
• Compared to whites, the likelihood of PAD is 55% lower among Chinese and 50% greater among African Americans [19]
• The femoral and popliteal arteries are affected in 80–90% of symptomatic PAD patients [18]
• The prevalence of amputation in PAD patients is 3–4% [19,20]