

Peripheral Arterial Disease in Patients with Type 2 Diabetes Mellitus

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Peripheral arterial disease (PAD) in patients with type 2 diabetes mellitus (T2DM) exhibits broad clinical characteristics and various consequences and is known as one of the major macrovascular complications of T2DM. Atherosclerosis is recognized as the most direct and important cause of PAD, but acute or chronic limb ischemia may be the result of various risk factors. In light of the increasing number of patients who undergo peripheral vascular procedures, the number of subjects who are exposed to the risks for PAD and related complications is increasing. In this review, we will discuss the clinical and epidemiological characteristics of PAD, as well as the clinical significance of PAD in T2DM subjects.

Keywords: Diabetes mellitus, type 2; Korea; Peripheral arterial disease

INTRODUCTION

Peripheral arterial disease (PAD) in people with type 2 diabetes mellitus (T2DM) exhibits broad clinical characteristics and various consequences and is known as one of the major macrovascular complications of T2DM, the prevalence of which is on the rise [1]. Atherosclerosis is recognized as the most direct and important cause of PAD, but acute or chronic limb ischemia may be induced by various risk factors [2].

Due to the increasing number of patients who undergo peripheral vascular procedures due to the aging of the overall population, the worldwide increase in T2DM prevalence, and developments in medical technologies, the number of subjects who are exposed to the risks for PAD and related complications is on the rise [3].

In this review, we will discuss the clinical and epidemiologic characteristics of PAD, as well as the clinical significance of PAD in T2DM subjects.

DEFINITION AND CLASSIFICATION

PAD is a general term for all vascular diseases that lead to abnormal function and structure of the aorta, its branches, and the lower-limb arteries secondary to atherosclerosis and thromboembolism-related pathophysiologies [4]. Typically, atherosclerosis decreases the size of the vascular lumen, leading to deficiencies in arterial perfusion without noticeable symptoms. However, depending on the degree of obstruction, various symptoms, including claudication, resting pain, ulceration, or gangrene, may occur during exercise [5].

PAD is typically classified according to clinical symptoms. The Fontaine and Rutherford classifications are the most well-known systems, under which increased stage describes severe symptoms (Table 1) [6-8]. PAD typically exhibits a chronic course but may be acutely exacerbated. Depletion of effective vascular volume by thrombosis, embolism, dehydration, and shock may be a cause of acute exacerbation of PAD [2]. This acute arterial occlusion is a fatal disease that requires emergent manipulations, such as amputation [4].

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EPIDEMIOLOGY

The prevalence of PAD is highly dependent on the definition of the diagnostic method. But, most studies on the prevalence of PAD among general populations used a low ankle-brachial index (ABI, ≤ 0.9) as a surrogate for PAD. From the analyses of National Health and Nutrition Examination Survey 1999 to 2004 in the United States, prevalence of low ABI was 5.9%, corresponding 7.1 million adults with PAD [9]. Excluding subjects with known cardiovascular disease, prevalence was 4.7% [9]. Similarly, a total of 5.8% of the United States population age

≥ 40 years had a low ABI or history of lower-extremity revascularization, representing 6.8 million people [10].

Prevalence of PAD was known diverse by ethnicity, with black people having the highest age-adjusted prevalence of low ABI [10,11]. Prevalence of low ABI is known to increase with age. In one study, prevalence of low ABI was 1.9% in the age group of 40 to 59 years, 8.1% in the group of 60 to 74 years, and 17.5% in the group of ≥ 75 years [11]. Although PAD is presumed to be more common in men, the prevalence of low ABI does not estimated to vary significantly by gender [12,13].

The PAD prevalence in T2DM subjects is unclear, but in the Framingham heart study, 20% of symptomatic PAD subjects also exhibited diabetes [14]. According to the the prevention of progression of arterial disease and diabetes (POPADAD) study, 20.1% of ≥ 40 -year-old patients with diabetes were associated symptoms exhibited PAD [15]. However, given that a large number of PAD patients are asymptomatic, it is assumed that more subjects with diabetes exhibit PAD. In the study conducted with 6,880 German people whose age ≥ 65 years, the prevalence of PAD by low ABI in diabetes subjects was 26.3%; whereas, prevalence of PAD in non-diabetic subjects was 15.3% [16]. Similar findings also have been reported [17,18].

In Korea, there has been no epidemiologic study on the prevalence of PAD in the total population, although a study was conducted in 14 university hospitals with approximately 1,400 ≥ 50 -year-old T2DM subjects exhibiting risk factors for PAD

Table 1. Classifications of peripheral arterial disease by clinical symptoms

Fontaine classification		Rutherford classification		
Stage	Clinical symptoms	Stage	Category	Clinical symptoms
I	Asymptomatic	0	0	Asymptomatic
IIa	Mild claudication	I	1	Mild claudication
IIb	Moderate to severe claudication	I	2	Moderate claudication
III	Ischemic rest pain	I	3	Severe claudication
IV	Ulceration or gangrene	II	4	Ischemic rest pain
		III	5	Minor tissue loss
		IV	6	Major tissue loss

Adapted from Korea National Diabetes Program, Clinical practice guideline for diabetic peripheral arterial disease [8].

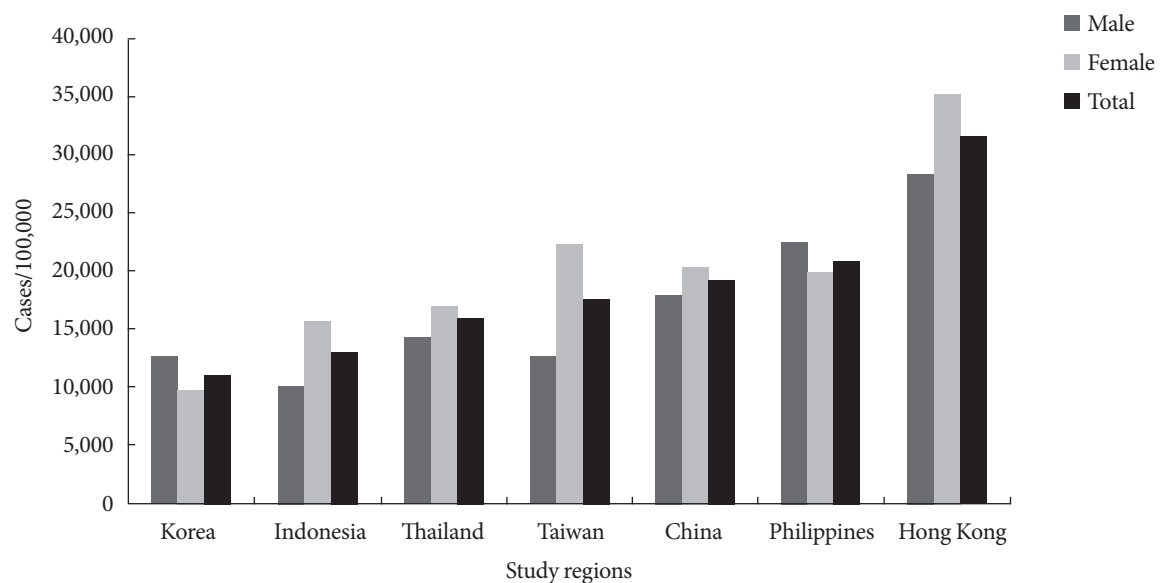


Fig. 1. Age- and gender-specific direct standardized prevalence of peripheral arterial disease in Asian patients with type 2 diabetes mellitus. Adapted from Rhee et al., with permission from Elsevier [19].

[19]. In this study, 11.9% of the subjects were found to exhibit PAD estimated by low ABI [19]. This prevalence was somewhat lower than that in other Asian regions (Fig. 1). Besides, there were some epidemiologic evidences which have investigated mainly in the university hospitals in Korea. In the previously diagnosed patients with coronary artery disease or cerebrovascular disease, prevalence of PAD by low ABI was estimated to be 7.8% [20]. In the prospective study among subjects with acute ischemic stroke or transient ischemic attack, prevalence of PAD by low ABI was 13.0% [21]. Additionally, prevalence of PAD by low ABI was 12.8% in the patients with previous percutaneous coronary intervention [22].

CLINICAL CHARACTERISTICS

Dyslipidemia, smoking, hypertension, and diabetes are known risk factors of PAD, similar to coronary artery disease [4,5,19,20,23]. These risks increase in patients who are ≥ 70 -year-old; in those who are 50- to 69-year-old with a history of diabetes or smoking; and in patients 40- to 49-year-old with diabetes and one or more atherosclerosis-related risk factor(s), intermittent claudication, abnormalities in pulse palpation of the lower limb or atherosclerosis in non-peripheral arteries (e.g., coronary, carotid, and renal artery) [2]. When a symptom of claudication appears, the symptom becomes aggravated in approximately 10% to 20% of patients in 5 years and advances to critical limb ischemia (CLI) in 1% to 2% of patients [2].

The clinical progression of PAD patients with diabetes is worse than that of those who are not. Lesions occur over a wider range of vasculature; the frequency of amputation was higher; and there was a significant difference in mortality [1,19]. In the results from multicenter study conducted by Asian subjects with type 2 diabetes, obesity, smoking, duration of diabetes and previous cardiovascular disease were identified as independent risk factors of PAD [19].

PAD is associated with cardiovascular disease [5,6]. Non-fatal myocardial infarction (MI) or stroke occurs in 20% of patients, and 15% to 30% of patients were died [24]. In the results from domestic study, subjects with previous history of coronary artery disease or cardiovascular disease had significantly higher prevalence of diabetes, dyslipidemia, renal insufficiency, and PAD with claudication [20]. CLI occurs in both lower limbs in 50% of patients at 1-year follow-up. CLI is accompanied by lower limb amputation in 25% and by cardiovascular disease in 25% [24,25].

DIAGNOSIS

The ABI is the standard for the diagnosis of PAD in clinical treatment or epidemiologic studies and represents a useful resource for the salvage of the lower limb, wound healing and survival prediction of patients [2,4]. ABI is calculated as the ratio of systolic blood pressure in the brachial artery to that in the posterior tibial artery after resting in a supine position, which is considered abnormal when it is below 0.90 [2,4]. When the diagnostic threshold was set to 0.90, the sensitivity of ABI for the diagnosis of PAD with $>50\%$ stenosis was 95%, and its specificity was 100% [26]. An ABI between 0.41 and 0.90 is evaluated as a mildly to moderately decreased blood flow, and an ABI <0.40 is evaluated as severely decreased blood flow [2,4]. In the recent meta-analysis, the pooled sensitivity and specificity of ABI ≤ 0.90 for PAD diagnosis were 75% and 86% and the pooled platelet lymphocyte ratio and neutrophil lymphocyte ratio were 4.18 and 0.29, respectively [27]. These results may mean that ABI is useful for identifying serious stenosis in clinical practice. However, in patients with diabetes, patients with distal lesions in elderly patients, and patients with mild stenosis less than 75%, diagnostic value of ABI was decreased [28].

Angiography is the most accurate test to examine vascular anatomy and pathology [3] and is, considered an essential evaluation tool prior to surgical management [3]. However, because angiography is an invasive procedure, risks such as bleeding, infection, and rupture as well as side effects associated with contrast media, such as hypersensitivity reaction and nephrotoxicity, may occur. In recent years, non-invasive imaging technologies have been developed, and ultrasound, multi-detector computed tomography (MDCT) and magnetic resonance (MR) angiography have been widely used [29-32]. Such non-invasive imaging modalities had reported comparable diagnostic and prognostic accuracy to conventional angiography [33,34]. In meta-analyses, sensitivity for detecting more than 50% stenosis or occlusion in MDCT was estimated 95%, and its specificity was 96%, and sensitivity for diagnosing segmental steno-occlusions for MR angiography was estimated 94.7% and specificity was 95.6% [31,35].

However, several limitations were also reported. We could observe decreased accuracy by intestinal gas, and decreased sensitivity in multivessel lesion in ultrasound imaging [36]. In MDCT images, the risk of contrast media induced nephrotoxicity is well known in the subjects with chronic kidney disease

[35]. Moreover, utility of MR angiography is limited for detection of in-stent restenosis, and risk of gadolinium induced nephrogenic systemic fibrosis is also concerned in the subjects with chronic kidney disease [36,37].

TREATMENT

The diagnosis of PAD necessitates the regulation of associated risk factors, medical treatment, and intervention of lesions in the lower limb. The management of risk factors of PAD is similar to the regulation of risk factors of disease in the coronary artery.

Exercise is known to be effective for the improvement of symptoms of claudication, the extension of walking distance to the aggravation of pain and the promotion of maximum oxygen consumption [3,4]. Walking exercise is typically recommended, and patients are asked to partake in this exercise at least three times a week for 30 to 45 minutes for 12 weeks or more [4]. A systematic review identified that compared exercise with usual care or placebo, exercise improved walking ability from 50% to 200%, and significantly improved maximal walking time, pain-free walking distance, and maximum walking distance [38].

Smoking cessation is very important advice for the treatment of PAD patients. The effects of cessation of smoking were studied in 343 patients with intermittent claudication [39]. The cumulative proportions with MIs after 10 years were 11% and 53%; the cumulative rates of cardiac deaths 6% and 43%; and the 10-year survival 82% and 46% among non-smokers and smokers, respectively [39]. For patients who have difficulty in stopping smoking on their own, varenicline, bupropion, and nicotine replacement therapy may be considered [4].

The management of associated diseases, such as diabetes, high blood pressure, and dyslipidemia, has an important impact on the clinical progress of PAD. In particular, meticulous foot care to prevent aggravation, crucial for clinical progress in diabetic patients, is recommended [40]. In diabetic patients, the general goal of blood glucose regulation is to achieve glycosylated hemoglobin <7%, but the goal of treatment is individualized for each patient's characteristics [41]. No controlled trials have directly evaluated the effects of glucose lowering on the natural history of PAD. The goal hypertension therapy is to achieve blood pressure below 140/90 mm Hg, and the use of angiotensin-converting enzyme inhibitor is preferentially considered [4]. There are no data evaluating whether treatment of

hypertension alters aggravation in patients with PAD. Nevertheless, hypertension should be controlled in such patients to reduce morbidity from cardiovascular disease [26]. The use of statins for dyslipidemia regulation is preferentially considered, which may be combined with fibric acid derivatives [4]. In a systemic review, specifically evaluated patients with lower limb PAD concluded that lipid-lowering therapy reduced disease progression, helped alleviate symptoms, and improved total walking times and pain-free walking distance [42].

There is an insufficient evidence to suggest a direct relationship between the use of antiplatelet agents and increases in pain or walking distance, but such agent have been proven to be significantly effective in decreasing the incidence of MI, stroke, or cardiovascular death; thus, low-dose aspirin (75 to 325 mg/day) is typically recommended. A systematic review found a similar reduction in mortality for patients with claudication treated with antiplatelet therapy compared with placebo [43]. Clopidogrel is a secondary drug recommended if aspirin cannot be used; 75 mg/day is recommended [3,4]. The clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE) trial found that clopidogrel 75 mg/day had a modest, but significant advantage over aspirin 325 mg/day for the prevention of stroke, MI, and PAD in subjects with a recent stroke, MI, or PAD [44]. Cilostazol is a phosphodiesterase inhibitor that impedes platelet aggregation and exhibits vasodilatory effect and improves dyslipidemia. Treatment with cilostazol for 24 weeks reportedly improved walking distance without claudication by approximately 54% on average compared with a placebo group or a group to which pentoxifylline was administered [45]. In a meta-analysis, the administration of 200 mg/day cilostazol for 12 to 24 weeks increased the maximum walking distance without claudication by up to 50% or 67% [46].

If patient symptoms do not improve despite proper drug treatment and rehabilitation, invasive procedures should be considered. If normal activities are not possible due to claudication and if the lesions exhibit minimal surgery-related risks and the intervention exhibits a high probability of success, re-perfusion should be attempted through a transcutaneous procedure or operation [2-4]. Early intervention is recommended when resting pain, ischemic ulceration, or necrosis is present. Balloon angioplasty and stent insertion are known to be effective in the alleviation of symptoms in many PAD patients [47,48]. In the past, the transcutaneous vascular procedure was used restrictively to cause stenosis of short lesions or occlusive lesions, but with advances in technology, transcutaneous vas-

cular intervention has been widely applied prior to the surgical procedure and widely attempted in patients in whom it is difficult to perform the surgical treatment. For the long-term success of transcatheter vascular intervention, the position and length of the lesions are important, and surgical treatment is preferred if the lesions are long, if there is stenosis in multiple areas, if the lesion is occlusive and if the lesion is calcified and stenotic [2-4].

Experimental or investigational agents for PAD include prostaglandins, naftidrofuryl, propionyl levocarnitine, defibrotide, ginkgo biloba, hyperbaric oxygen, and angiogenic growth factors [49]. Naftidrofuryl can be used for treatment of claudication, and it has known to have fewer side effects than cilostazol [26]. However, there had not been any large scale, randomized trial for relevant treatment, and more clear evidences are required for extensive clinical application.

CONCLUSIONS

As PAD becomes an increasingly important complication in T2DM subjects, a deeper understanding of the related diseases and the establishment of a standardized method of treatment is particularly important. Indeed, PAD confers poorer prognosis in T2DM patients compared with nondiabetic patients, and early diagnosis, management and positive treatment are necessary. However, with the exception of a few epidemiological studies, there is a lack of data concerning Korean type 2 diabetes patients, and more strategies for the diagnosis and treatment of PAD based on empirical evidence are needed.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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