

Prevalence and Risk Factors for the Peripheral Neuropathy in Patients with Peripheral Arterial Occlusive Disease

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Purpose: Peripheral neuropathy (PN) is known as a major contributor of the worsening of ischemic symptoms and the foot ulceration in patients with peripheral arterial occlusive disease (PAOD). However, there are few studies reporting the prevalence and risk factors for PN in PAOD. This study aimed to evaluate these issues for PN and to establish the importance of screening as additional treatment target for PN in PAOD.

Materials and Methods: A total of 52 limbs with PAOD were enrolled from January 2011 to December 2012. PN was divided into radiculopathy, ischemic PN (IPN), and diabetic PN (DPN), based on electromyographic findings. We investigated the prevalence of overall PN and subtypes of PN and then analyzed the risk factors.

Results: The prevalence of overall PN in PAOD was 43 of 52 limbs (82.7%). In terms of subtypes of PN, the prevalence rate of radiculopathy and IPN was 30.8% and 23.1%, respectively. DPN showed in 22 limbs (73.3%) among 30 diabetic limbs. There was no significant correlation between each type of PN and ischemic symptoms. Our analysis showed that coronary artery disease (CAD) was a significant risk factor ($P=0.01$) for IPN, however, did not identify any significant risk factors for DPN.

Conclusion: This present study indicated that most patients with PAOD had PN and CAD was a risk factor for IPN. In particular, PAOD with diabetes represented a higher prevalence for DPN. Our study suggests that PN should be evaluated and considered as another treatment target in patients with PAOD.

Key Words: Peripheral arterial occlusive disease, Prevalence, Peripheral, neuropathy, Risk factor

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INTRODUCTION

Peripheral arterial occlusive disease (PAOD) is a chronic atherosclerotic process that causes narrowing of the peripheral arterial vasculature, predominantly in the lower limbs. It has an estimated worldwide prevalence of up

to 10%, increasing to nearly 30% in patients more than 50 years [1]. Moreover, several significant risk factors for the development of PAOD, including hypertension (HTN), diabetes mellitus (DM), coronary artery disease (CAD), cerebrovascular disease (CVD), smoking, hypercholesterolemia, among others, have been reported and

identified by a well-defined prospective study [2].

In addition, PAOD is known as a major cause of critical limb ischemia (CLI) and limb amputation, although not all limbs with PAOD develop CLI. Some studies have reported the occurrence of peripheral neuropathy in patients with PAOD and described that PAOD causes axonal degeneration, resulting in axonal polyneuropathy [3,4]. Macroangiopathy and microangiopathy in PAOD may lead to ischemic polyneuropathy of the lower extremities, mainly due to ischemic tissue damage [4]. It is well known that the damage of somatic and autonomic nerve fibers occurs in PAOD independently from the effects of chronic ischemia of the limbs [5,6]. Therefore, the ischemia-associated peripheral neuropathy may contribute to the functional impairment and CLI observed in patients with PAOD [7-9]. DM also causes peripheral neuropathy and the vasculoneuropathic limbs represented in DM and PAOD affect peripheral nerve conduction, including the sensory, motor, and autonomic nerves [10,11]. Consequently, diabetic peripheral neuropathy becomes a major contributor to diabetic foot ulcers.

However, there are few studies reporting the overall prevalence and risk factors for peripheral neuropathy in patients with PAOD. We performed a prospectively-designed study to investigate the prevalence of peripheral neuropathy in PAOD and retrospectively reviewed subjects' medical records to analyze the risk factors for peripheral neuropathy in 52 limbs with PAOD. Therefore, this study aimed to identify the prevalence and the risk factors for

peripheral neuropathy and to confirm the importance of screening as additional treatment target for peripheral neuropathy in patients with PAOD.

MATERIALS AND METHODS

From January 2011 to December 2012, 39 patients (60 limbs) with PAOD were recruited and consented to this study. Among these patients, four patients (8 limbs) who were unable to perform the electromyography (EMG) were excluded. Therefore, a total of 52 limbs with PAOD were enrolled and analyzed for the prevalence and risk factors of peripheral neuropathy. This present study received the approval of the institutional review board of Seoul Medical Center (IRB No. 2011 1 009) and the written consent from all the patients for participation was obtained.

In this study, the enrollment of all PAOD patients was based on the findings of lower extremity computed tomography (CT) angiography that showed at least one significant stenotic or occlusive lesion of the iliac arteries and femoropopliteal arteries (Fig. 1). In addition, peripheral neuropathy was divided into radiculopathy (Fig. 2), ischemic peripheral neuropathy, and diabetic peripheral neuropathy (Fig. 1), based on the findings of EMG. EMG techniques provided the most valuable diagnostic information in this study. Our EMG examination was composed of two main tests: nerve conduction studies (NCS) and needle EMG. The three types of NCS were compound muscle action potential, sensory nerve action potential and mixed nerve action

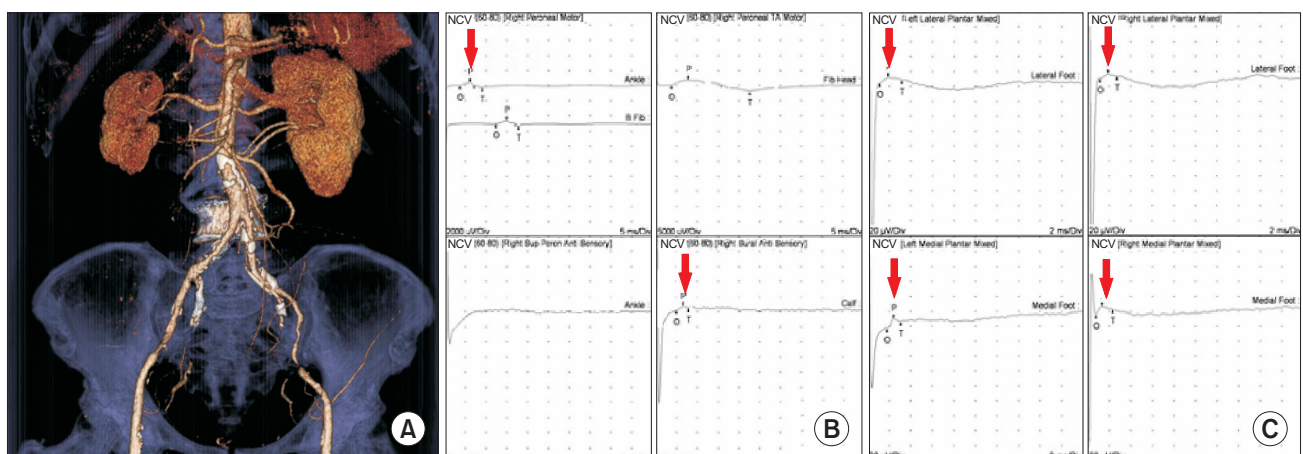


Fig. 1. Computed tomography (CT) angiographic and electromyographic (EMG) findings in patients with peripheral arterial occlusive disease and ischemic/diabetic peripheral neuropathy. (A) CT angiographic findings indicate diffuse calcification of aortoiliac arteries and stenotic/occlusive lesions of both external iliac arteries. (B) EMG indicates decreased amplitude and conduction velocity (red arrows) of right peroneal compound muscle action potential and decreased amplitude of right sural sensory nerve action potential (SNAP) in patients with peripheral arterial occlusive disease and ischemic peripheral neuropathy. (C) EMG indicates decreased amplitude (red arrows) of bilateral medial and lateral plantar SNAP in patients with peripheral arterial occlusive disease and diabetic peripheral neuropathy.

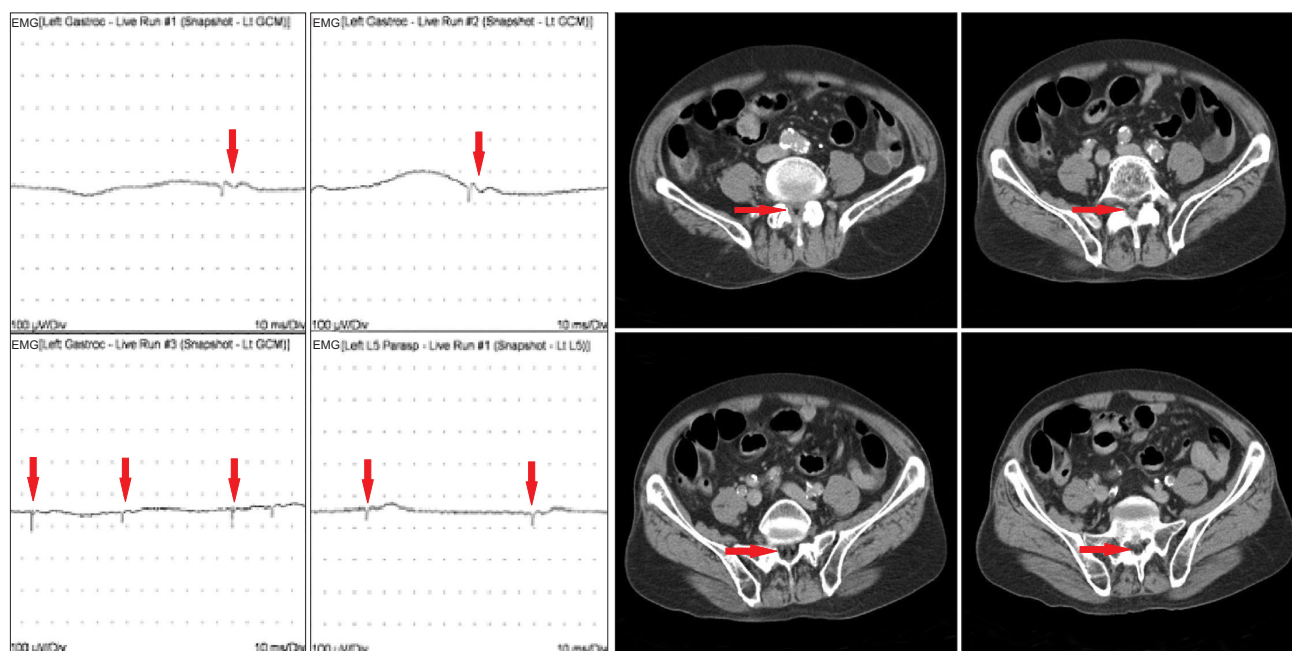


Fig. 2. Electromyographic (EMG) and non-contrast computed tomography (CT) findings in patients with peripheral arterial occlusive disease and radiculopathy. EMG indicates the denervation potential (red arrows) in the left L5 paraspinalis and the left medial head of gastrocnemius. Non-contrast CT findings indicate the narrowing of the L4–5 spinal canal (red arrows) with impingement of the cauda equina.

potential, and were analyzed for amplitude, duration, latencies and conduction velocity. These tests were used in diagnosing peripheral polyneuropathies (ischemic peripheral neuropathy, and diabetic peripheral neuropathy) [12]. In contrast, needle EMG registered signs of denervation: fibrillation potentials, decreased recruitment, and long-duration, high-amplitude polyphasic motor unit action potential. Needle EMG was the most sensitive and specific electrodiagnostic test for identifying radiculopathies [13]. The clinical and imaging findings of all enrolled patients supported to design the most appropriate electrodiagnostic study and to conclude findings of EMG. Lumbar magnetic resonance imaging (MRI) was occasionally performed in patients with histories of back pain. The findings of CT angiography were reviewed independently by two radiologists and the EMG was reviewed by two rehabilitation medicine doctors. Subsequently, we evaluated the clinical manifestations of the patients on admission, as well as their in-hospital and long-term clinical outcomes post-treatment.

The patients with PAOD were classified into non-neuropathic and neuropathic groups. Moreover, demographic features and risk factors were recorded, including: age, gender, Trans-Atlantic Inter-Society Consensus (TASC) classification, location (proximal vs. distal), ischemic symptoms (asymptomatic, intermittent claudication, rest pain, and ulcer/gangrene), HTN, DM, CAD, chronic

kidney disease (CKD), smoking status, DM medication, statin usage and spinal stenosis (Table 1). The locations of PAOD were defined as proximal when the iliac arteries were involved, and distal when the femoropopliteal arteries were involved.

In this study, we first investigated the prevalence of overall peripheral neuropathy and then evaluated each type of peripheral neuropathy in patients with PAOD. We compared the demographic features between the non-neuropathic group and the neuropathic group by chi-square test or Fisher's exact test. In addition, we analyzed the risk factors that had statistically significant correlations with each type of peripheral neuropathy, using a logistic regression model. Multivariate analysis was used to estimate the odds ratios for the correlation between neuropathy and the risk factors with 95% confidence interval. A P-value <0.05 was considered to indicate significance. Statistical analyses were carried out with PASW Statistics ver. 18.0 (IBM Co., Armonk, NY, USA).

RESULTS

1) Overall prevalence for peripheral neuropathy

In this study, the overall prevalence of peripheral neuropathy in patients with PAOD was 43 (82.7%) of 52 limbs (Table 1). The distal location (femoropopliteal lesion)

Table 1. Comparison of clinical characteristics between non-neuropathic limbs (n=9) and neuropathic limbs (n=43) in patients with peripheral arterial occlusive disease

Clinical characteristic	Non-neuropathy (n=9, 17.3%)	Neuropathy (n=43, 82.7%)	P-value ^a
Age (y)	71.33±4.12	70.71±8.61	0.48
Age ≥70	6 (66.7)	22 (51.2)	
Male	9 (100)	39 (90.7)	1.00
TASC classification			0.23
TASC A	6 (66.7)	14 (32.6)	
TASC B	2 (22.2)	11 (25.5)	
TASC C	1 (11.1)	14 (32.6)	
TASC D	0 (0)	4 (9.3)	
Location			0.05
Proximal (aortoiliac)	5 (55.6)	9 (20.9)	
Distal (femoropopliteal)	4 (44.4)	34 (79.1)	
Ischemic symptoms			0.15
Asymptomatic	1 (11.1)	2 (4.7)	
Intermittent claudication	7 (77.8)	19 (44.2)	
Critical limb ischemia	1 (11.1)	22 (51.2)	
Rest pain	1 (11.1)	8 (18.6)	
Ulcer/gangrene	0 (0)	14 (32.5)	
Comorbidities			
Hypertension	7 (77.8)	35 (81.4)	1.00
Diabetes mellitus	5 (55.6)	25 (58.1)	1.00
Coronary arterial disease	0 (0)	16 (37.2)	0.04
Cerebrovascular disease	1 (11.1)	7 (16.3)	1.00
Chronic kidney disease	1 (11.1)	9 (20.9)	0.67
Smoking	6 (66.7)	22 (51.2)	0.48
Spinal stenosis	9 (100)	29 (67.4)	0.09
Statin usage	2 (22.2)	16 (37.2)	0.47

Values are presented as mean±standard deviation or number (%).

TASC, Trans-Atlantic Inter-Society Consensus.

^aChi-square test or Fisher's exact test.

of PAOD and the presence of CAD showed statistically significant differences between the non-neuropathic limbs and the neuropathic limbs (Table 1). In addition, all amputations (6 limbs, 11.5%) were performed in patients with peripheral neuropathy. In terms of the subtypes of peripheral neuropathy, the prevalence of radiculopathy and ischemic peripheral neuropathy was 16 (30.8%) and 12 (23.1%) of 52 limbs, respectively. Among the 30 diabetic limbs, diabetic peripheral neuropathy showed in 22 limbs (73.3%). However, there was no neuropathic limb that was combined with all subtypes of peripheral neuropathy.

2) Radiculopathy

Among all enrolled limbs, the prevalence rate of radiculopathy on EMG findings was 30.8% and radiculopathy was 37.2% in the group of 43 neuropathic limbs. Among the total of 3 asymptomatic limbs, 2 limbs showed radiculopathy on EMG findings. In addition, non-contrast CT showed lumbar spinal stenosis in 71.4% (25 patients) of

all patients (Fig. 2).

3) Ischemic peripheral neuropathy

Ischemic peripheral neuropathy was found in 23.1% (12 limbs) of a total of 52 limbs and 30.4% (7 limbs) of 23 CLI limbs (Table 2). However, ischemic symptoms and TASC classification did not show any statistically significant differences between non-ischemic neuropathic limbs and ischemic neuropathic limbs (P=0.50 and P=0.60, respectively) (Table 2). In addition, the amputation rates of the non-ischemic neuropathic limbs (n=40) and the ischemic neuropathic limbs (n=12) were 7.5% and 25%, respectively, and there was no statistically significant difference between the two groups (P=0.13). Our statistical analyses showed that CAD was a significant risk factor (P=0.01, odds ratio 56.2) for the presence of ischemic peripheral neuropathy (Table 2).

Table 2. Prevalence and risk factors for ischemic peripheral neuropathy in patients with peripheral arterial occlusive disease (n=52)

Risk factor	Non-IPN (n=40, 76.9%)	IPN (n=12, 23.1%)	Univariate ^a		Multivariate ^b
			P-value	P-value	OR (95% CI)
Age (y)	70.7±7.9	71.8±8.2	0.72	0.05	10.30 (1.01-105.32)
Age ≥70	21 (52.5)	7 (58.3)			
TASC classification			0.60	0.41	0.64 (0.22-1.85)
TASC A	16 (40.0)	4 (33.3)			
TASC B	9 (22.5)	4 (33.3)			
TASC C	11 (27.5)	4 (33.3)			
TASC D	4 (10.0)	0 (0)			
Location			0.30	0.85	0.77 (0.05-11.93)
Proximal (aortoiliac)	12 (30.0)	2 (16.7)			
Distal (femoropopliteal)	28 (70.0)	10 (83.3)			
Ischemic symptoms			0.50	0.09	3.65 (0.81-16.36)
Asymptomatic	3 (7.5)	0 (0)			
Intermittent claudication	22 (55.0)	4 (33.3)			
Critical limb ischemia	15 (37.5)	8 (66.7)			
Rest pain	7 (17.5)	2 (16.7)			
Ulcer/gangrene	8 (20.0)	6(50)			
Comorbidities					
Hypertension	32 (80.0)	10 (83.3)	0.58	0.68	0.56 (0.03-9.24)
Diabetes mellitus	27 (67.5)	3 (25.0)	0.02		
Coronary arterial disease	9 (22.5)	7 (58.3)	0.03	0.01	56.18 (3.75-842.23)
Cerebrovascular disease	6 (15.0)	2 (16.7)	0.60	0.52	0.37 (0.02-7.73)
Chronic kidney disease	6 (15.0)	4 (33.3)	0.16	0.72	1.65 (0.11-26.01)
Smoking	22 (55.0)	6 (50.0)	0.76	0.75	0.74 (0.11-4.76)
Statin usage	14 (35.0)	4 (33.3)	0.60	0.13	5.29 (0.63-44.88)

Values are presented as mean±standard deviation or number (%).

IPN, ischemic peripheral neuropathy; TASC, Trans-Atlantic Inter-Society Consensus; OR, odds ratio; CI, confidence interval.

^aChi-square test or Fisher's exact test, ^blogistic regression model.

4) Diabetic peripheral neuropathy

Of the 30 total diabetic limbs, diabetic peripheral neuropathy was identified in 22 limbs (73.3%) (Table 3). The combined neuropathy of ischemic peripheral neuropathy and diabetic peripheral neuropathy showed in 3 limbs (10%) of the diabetic limbs. There was no statistical significance between diabetic peripheral neuropathy and ischemic symptoms (P=0.16) (Table 3). Although the diabetic limbs requiring insulin therapy showed higher rates of peripheral neuropathy, there was no statistically significant correlation in terms of the types of DM management (P=0.15). In addition, all patients with CVD or CKD had diabetic peripheral neuropathy in their ischemic limbs. However, the multivariate analysis for risk factors of diabetic peripheral neuropathy did not identify any statistically significant risk factors in this study (Table 3).

DISCUSSION

Unfortunately, there are few studies investigating the prevalence of overall peripheral neuropathy, including radiculopathy, ischemic peripheral neuropathy, and diabetic neuropathy, in patients with PAOD. Peripheral neuropathy leads to numbness and pain in the lower extremities and may contribute to disabilities [14]. If the ischemic symptoms of PAOD are associated with neuropathy, these combined vasculoneuropathic symptoms might cause the limb symptoms to persist despite an appropriate treatment for PAOD. In this study, we found that the majority of patients with PAOD have some type of peripheral neuropathy (82.7%). These findings support assessing the peripheral nervous system in the lower extremities as an essential step to designing a treatment plan for patients with PAOD.

The leg symptoms due to radiculopathy, mainly caused by the compression of the spinal nerve root, must be di-

Table 3. Prevalence and risk factors for diabetic peripheral neuropathy in patients with diabetes mellitus and peripheral arterial occlusive disease (n=30)

Risk factor	Non-DPN (n=8, 26.7%)	DPN (n=22, 73.3%)	Univariate ^a		Multivariate ^b
			P-value	P-value	OR (95% CI)
Age (y)	70.5±7.8	70.0±7.9	0.49	0.92	1.20 (0.04-38.09)
Age ≥70	4 (50.0)	9 (40.9)			
TASC classification			0.74	0.82	0.86 (0.23-3.27)
TASC A	4 (50.0)	7 (31.8)			
TASC B	1 (12.5)	6 (27.3)			
TASC C	2 (25.0)	7 (31.8)			
TASC D	1 (12.5)	2 (9.1)			
Location			0.10	0.58	2.25 (0.13-38.14)
Proximal (aortoiliac)	3 (37.5)	2 (9.1)			
Distal (femoropopliteal)	5 (62.5)	20 (90.9)			
Ischemic symptoms			0.16	0.72	1.33 (0.29-6.17)
Asymptomatic	1 (12.5)	0 (0)			
Intermittent claudication	5 (62.5)	11 (50.0)			
Critical limb ischemia	2 (25.0)	11 (50.0)			
Rest pain	0 (0)	6 (27.3)			
Ulcer/gangrene	2 (25.0)	5 (22.7)			
Comorbidities					
Hypertension	7 (87.5)	19 (86.4)	0.72	0.73	2.04 (0.04-118.74)
Diabetes mellitus	1 (12.5)	9 (40.9)	0.15	0.47	3.10 (0.15-64.38)
Coronary arterial disease	1 (12.5)	10 (45.5)	0.11	0.42	5.49 (0.09-332.48)
Cerebrovascular disease	0 (0)	4 (18.2)	0.27		
Chronic kidney disease	0 (0)	6 (27.3)	0.13		
Smoking	5 (62.5)	10 (45.5)	0.34	0.78	0.72 (0.07-7.01)
Statin usage	4 (50.0)	11 (50.0)	0.66	0.61	2.12 (0.12-38.82)

Values are presented as mean±standard deviation or number (%).

DPN, diabetic peripheral neuropathy; TASC, Trans-Atlantic Inter-Society Consensus; OR, odds ratio; CI, confidence interval.

^aChi-square test or Fisher's exact test, ^blogistic regression model.

fferentiated from the ischemic symptoms due to PAOD [15]. In this study, EMG was used to confirm the presence of radiculopathy in patients with PAOD and showed that approximately one third of the ischemic limbs had radiculopathy. In addition, spinal stenosis is a degenerative disease that is frequently associated with the elderly and Uesugi et al. [16] reported that 6.7% of patients with lumbar spinal stenosis had peripheral arterial disease. On the contrary to this issue, our MRI findings found that more than two-thirds of PAOD patients had lumbar spinal stenosis. Therefore, lumbar spinal stenosis in PAOD should be evaluated as coexisting disease and treated appropriately.

The diagnosis of ischemic peripheral neuropathy has been challenging and is easily confused with diabetic peripheral neuropathy [17]. Therefore, our present study evaluated the relatively relevant ischemic peripheral neuropathy using EMG. In addition, to analyze the risk

factors for ischemic neuropathy, DM was excluded as a risk factor due to the overriding influence of DM on peripheral nerve function [7]. The multivariate analysis revealed that the presence of CAD was a statistically significant risk factor for ischemic peripheral neuropathy. This finding implied that concomitant PAOD and CAD should warrant an investigation regarding the presence of ischemic peripheral neuropathy. In addition, peripheral nerves have a dual blood supply (an intrinsic system comprised of longitudinal microvessels and an extrinsic system of regional arteries) so they do not easily suffer ischemic damage [18]. This ischemia-resistant nature of peripheral nerves might contribute to the relatively lower prevalence rate for ischemic neuropathy (27.3%), even in CLI limbs.

Diabetic peripheral neuropathy, defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with DM after the exclusion of other causes [19,20], has been known as one of the most common DM-related

complications, affecting up to two-thirds of patients with DM [21–23]. In addition, diabetic peripheral neuropathy frequently coexists with PAOD and might alter and worsen the ischemic symptoms [24]. Our study also showed a higher prevalence of diabetic peripheral neuropathy (73.3%) in diabetic limbs with PAOD. Furthermore, diabetic peripheral neuropathy usually affects the sensory and motor components of peripheral nerves, as well as the autonomic nervous system. Therefore, in conjunction with ischemia, the diabetic neuropathic foot is vulnerable to unattended minor injuries due to the sensory neuropathy and foot deformities caused by motor neuropathy [25]. These conditions may cause foot ulceration and may make the foot more susceptible to infection, increasing the probability of amputation, especially in combination with ischemia [26]. However, this study did not find a statistically significant correlation between diabetic peripheral neuropathy and leg ischemic symptoms. The higher rate of peripheral neuropathy in patients with DM and PAOD could be influenced by the co-morbidities and duration of DM, as these factors are the major determinants of PAOD in patients with type 2 DM [7]. In the present study, most ischemic limbs with co-morbidities for PAOD had diabetic peripheral neuropathy but did not show a statistical significance under univariate and multivariate analyses. Although our study did not determine a statistically significant risk factor for diabetic peripheral neuropathy, it has been established that most patients with DM and PAOD, especially patients with co-morbidities for PAOD and long-standing DM, have diabetic peripheral neuropathy. Consequently, the present study suggests that electrophysiologic tests are needed to confirm and to manage diabetic peripheral neuropathy in patients with DM and PAOD.

The present study has several limitations. The major limitation was the small number of the patients with PAOD. Therefore, our study found a higher rate of overall peripheral neuropathy in patients with PAOD but failed to

identify risk factors for each type of peripheral neuropathy. Second, EMG is a useful diagnostic test for the diagnosis of radiculopathy and diabetic neuropathy; however, its findings make it difficult to differentiate ischemic peripheral neuropathy from diabetic peripheral neuropathy in patients with PAOD. In this study, the relatively lower prevalence of ischemic neuropathy, even in CLI, might be caused by the differentiation difficulty from diabetic peripheral neuropathy and the ischemia-resistant nature of peripheral nerves. Third, the outcomes of neuropathic limbs in patients with PAOD could not be evaluated due to its small sample size and inconsistent treatment strategies for PAOD.

CONCLUSION

In summary, our findings indicated that most patients with PAOD had some type of peripheral neuropathy, and the presence of CAD was analyzed as a risk factor for ischemic peripheral neuropathy in patients with PAOD. In particular, concomitant DM and PAOD represented a relatively higher prevalence rate for diabetic peripheral neuropathy but the statistical analyses did not determine the risk factors for diabetic neuropathy.

Most vascular specialists have been focusing on diagnosing and treating various stenotic/occlusive lesions to improve leg symptoms and to prevent amputation; however, peripheral neuropathy in conjunction with PAOD is also the major determinant for leg symptoms and disabilities. Our present study suggests that the presence of peripheral neuropathy might be a common situation in patients with PAOD, therefore peripheral neuropathy should be evaluated and considered as another treatment target in PAOD.

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