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Mini Review

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The Relationship between Peripheral Arterial Disease and Chronic Obstructive Pulmonary Disease

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a representative chronic pulmonary disease and is predicted to become the third leading cause of death in middle-income countries by 2030.[1] COPD has been recognized not only as a lung but also a systemic disease.[2] Smoking is a major cause of COPD, cardiovascular disease,[3] stroke[4] and peripheral arterial disease (PAD). Smoking-induced inflammation and other risk factors like dyslipidemia cause vascular endothelial damage *via* oxidative stress, and a vicious cycle with the characteristics of atherosclerosis ensues.[5] Recent studies paid particular focus on PAD as COPD comorbidities because it has been unclear that prevalence of PAD in COPD patients.

PAD stems from atherosclerosis and encompasses a range of noncoronary arterial syndromes which are caused by altered structure and function of arteries that provide blood supply to the brain, visceral organs, and the limbs.[6] Major risk factors of PAD are diabetes mellitus, smoking, hypertension, hyperlipidemia, and kidney dysfunction.[7] Ankle-brachial index (ABI) is the primary noninvasive evaluation to diagnose PAD.[8] An ABI of ≤0.90 was demonstrated to be highly sensitive and specific for PAD diagnosis.[9] Many PAD patients exhibit no symptoms, and the ratio of symptomatic to asymptomatic PAD patients was reported to be 1:3.[8] Fontaine classification is often used to explain PAD symptoms (Table 1). Intermittent claudication is a classic symptom complex in patients with PAD and manifests as exercise-induced discomfort in the lower limbs that is relieved on rest. Both Fontaine class III and IV PAD is characterized by critical limb ischemia characterized by end-stage PAD with pain provoked at rest or tissue loss.

PREVALENCE OF PAD IN PATIENTS WITH COPD

The reported prevalence of PAD in COPD patients ranges widely, from 8.0% to 81.4%. (Table 2). The recent large-scale observational COPD and Systemic Consequences-Comorbidities Network (COSYCONET) study reported by Houben-Wilke et al[10] recruited 2,741 patients with COPD, with 2,088 included in final analyses. The prevalence of PAD was higher in patients with COPD than in those with non-COPD among the age- and sex-matched cohort (8.8% *vs*. 1.8%-2.6%, respectively). Even when smoking status was matched, the prevalence of PAD was higher than in patients with COPD than in those with non-COPD (7.7% *vs*. 2.6%, respectively). PAD is more prevalent in patients with more severe COPD (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage I-IV: 5.1%, 7.4%, 11.1%, and 9.5%, respectively). Moreover, functional capacity evaluated by the six-minute walking test was significantly lower in COPD patients with PAD than those without PAD (256 m *vs*. 422 m, $p<0.001$). Furthermore, health status evaluated by the COPD-specific St. George's Respiratory Questionnaire, COPD Assessment Test, and EuroQol-5 Dimensions questionnaire was significantly worse in COPD patients with PAD than those without PAD. However, the rate of COPD in PAD patients is currently not known, which warrants future investigation.

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Table 1: Fontaine Classification.

Stage	Clinical symptoms
I	Asymptomatic
IIa	Mild claudication
IIb	Moderate to severe claudication
III	Ischemic rest pain
IV	Ulceration or gangrene

RELATIONSHIP BETWEEN COPD AND ASYMPTOMATIC PAD

Understanding asymptomatic PAD is critical for early intervention. In the COSYCONET study, more than two-thirds of COPD patients with PAD were diagnosed during the study. Similarly, Pecci et al reported that 84 patients (36.8%) had abnormal ABI (<0.9) and that 49 patients (70.9%) were asymptomatic for PAD among 246 COPD patients.[11] Thus, the majority of PAD in COPD patients are predicted to be asymptomatic. Hooi et al reported that asymptomatic PAD was significantly associated with cardiovascular morbidity (hazard ratio [HR] 1.6, 95% confidence interval [CI] 1.3-2.1), total mortality (HR 1.4, 95% CI 1.1-1.8), and cardiovascular mortality (HR 1.5, 95% CI 1.1-2.1).[12] McDermott et al reported that even in patients with asymptomatic PAD, a lower ABI level was associated with impaired lower extremity functioning such as walking speed and standing balance.[13] Mohler et al reported that 35% of lower limbs had developed new lower extremity arterial lesions and that 26% of patients developed new intermittent claudication one year after diagnosis.[14] Therefore, COPD patients should be evaluated for early detection of PAD as even asymptomatic PAD impacts durability, muscle strength, mortality, and symptom progression.

CONCLUSION

In this mini-review, we outlined the association of COPD with PAD. Increased prevalence of PAD in COPD patients may be caused by COPD disease itself including systemic inflammation rather than by smoking status. PAD is associated with worse functional capacity and health status in COPD patients. Clinicians should evaluate COPD patients for PAD to identify their functional impairment and health status as well as their risk for cardiovascular disease and stroke.

Table 2: Prevalence of PAD in Patients with COPD.

Author	Country	n	Age (years)	Definition of PAD	Prevalence (%)	Lung function
Castagna et al[15]	France	151	67	ABI <0.9	81.4	FEV_1 37% FEV_1 /FVC 47%
Blum et al[16]	Israel	87	69.8	ABI <0.9	31	FEV_1 with PAD 34% FEV_1 without PAD 45%
Pecci et al[11]	Spain	246	70.2	ABI <0.9	36.8	FEV_1 with PAD 46% FEV_1 without PAD 52%
Lin et al[17]	Taiwan	427	70	ABI <0.9	8	FEV_1 with PAD 51.8% FEV_1 without PAD 51.1%
Matsuoka et al[18]	Japan	55	72.4	ABI <0.9	9.8	FEV_1 47.2%
Sun et al[19]	Taiwan	200	70.9	ABI <0.9	8.5	FEV_1 with PAD 55.9% FEV_1 without PAD 56.5%
Chakrabortyet al[20]	India	115	68.02	ABI <0.9	29.57	FEV_1 with PAD 51.8% FEV_1 without PAD 51.1%
Houben-Wilke et al[10]	Germany	2088	65.3	ABI <0.9	8.8	FEV_1 with PAD 48.4% FEV_1 without PAD 53.4%

PAD: Peripheral Arterial Disease; ABI: Ankle-Brachial Index; FEV_1: Forced Expiratory Volume-One Second; FVC: Forced Vital Capacity.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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