



Peripheral arterial stenosis and coronary artery disease coincidence

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ABSTRACT

Atherosclerosis is a chronic slow-developing condition affecting medium-size and large blood vessels. It is the principal underlying pathology of coronary heart disease and stroke. In some countries, coronary artery disease (CAD) is the cause of nearly half (48%) of the deaths and, loss of productivity life. Peripheral arterial disease (PAD) is defined as atherosclerosis in peripheral arteries instead of coronary arteries. CAD and PAD have same risk factors and underlying pathophysiological processes. Therefore, patient with CAD should be considered for PAD. Ankle brachial index (ABI), duplex sonography, and some other non-invasive techniques are recommended for PAD diagnosis in patients with the history of CAD. Pharmacotherapy, endovascular interventions, and surgical management could be chosen according to the patient's situation. Cardiologists and general practitioners should consider PAD in a patient with CAD or DM as a strong correlated disease.

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Introduction

Atherosclerosis and coronary artery disease (CAD)

The term arteriosclerosis was first introduced by Johann Lobstein in 1833 explaining the clinical-pathologic relationship between infarction and atherosclerosis (1,2).

Atherosclerosis is a chronic slow-developing condition affecting medium-size and large blood vessels. It is the principal underlying pathology of coronary heart disease and stroke. It is initially an inflammatory response to various forms of endothelial injury associated with vascular smooth muscle cell proliferation (3).

Atherosclerosis major risk factors

Age, male sex, heredity, high blood pressure, high blood cholesterol levels, diabetes mellitus, smokings, socioeconomic conditions, and being overweight are well-established risk factors for

atherosclerosis (4,5). Scientists concluded that increased atherosclerosis will lead to increase in serum total cholesterol (TC) which might cause the increase in CAD in the Asian countries (6).

A reduction in levels of plasma HDL-C is associated with elevated risk of atherosclerotic disease. Moreover, most of the patients with CAD possess low HDL-C levels. On the other hand, LDL-C has several major risk factors including age, low HDL-C (<40 mg/dL), cigarette smoking, hypertension (BP>140/90 mm Hg), diabetes, family history of premature CAD (7). Delavar et al. have comprehensively studied the status of dyslipidemia in Iran. Their report stated that the TC≥240 mg/dl was in 11.4%, and triglyceride ≥150 mg/dl in 41.5%, HDL-C<40 mg/dl in 17.0% and >60 mg/dl in 24.7%, and 130<LDL-C<159 mg/dl in 16.6%, and >160 mg/dl in 7.5% of patients (8).

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High blood pressure (HBP) is another risk factor for CAD. According to WHO, about 600 million people suffer from HBP are at risk of heart attack, stroke, and cardiac failure. It is estimated that 7.1 million deaths globally are due to HBP that is about 13 percent of the global fatality. Researches indicated that about 62 percent of strokes and 49 percent of heart attacks were caused by HBP (9).

CAD causes more than half of (60%) all mortality in individuals with diabetes. In people with type 1 or type 2 diabetes, the risk of cardiovascular events increases 2-3 times and is higher in women (10).

Smoking is another risk factor for CAD, American Heart Association (AHA) estimates that the number of smokers are 1.3 billion and it will rise to 1.7 billion by 2025 worldwide if the global prevalence of tobacco use remains unchanged (11). AHA reports that use of tobacco kills 5.4 million people each year worldwide. It predicts that tobacco-related deaths will significantly increase to more than 8 million deaths a year by 2030. Some 80% of those deaths will occur in the developing countries (12).

Pathophysiology of atherosclerosis

Atherosclerosis is characterized by the accumulation of fat and cholesterol, lipoprotein oxidation, inflammation, cellular rubbish outcomes calcium, wound tissue, and other substances developed within the inner lining of arteries (13). It is also related to infiltration of mononuclear cells and smooth muscle generation (14). Complicated pathological process in blood vessels walls progresses over many years. Cholesterol and fatty materials remain inside the lumen of arteries and form plaques. These plaques or deposits make the inner surface of the blood vessels to be irregular and lead to narrow the lumen, thus blood flows through them with difficulty. Therefore, blood vessels become less flexible and the plaque can rupture and lead to the formation of a blood clot. The blood clot can develop in a coronary artery; in this case, it can result in a heart attack. In addition, the blood clot can form in the brain, which can lead to a stroke (15).

Atherosclerosis and inflammation

Atherosclerosis is also associated with innate and acquired immune responses that start in the early years of life and it becomes clinically apparent in later life (16-19). The role of inflammation in atherosclerosis has been known over three decades ago. Several studies confirmed that inflammatory mechanisms performed an important part in atherosclerosis and the initial stages accompanied by inflammation (20,21).

Recently, researchers demonstrated that characterization of low-grade systemic inflammation

can be carried out by an increase (usually two- to threefold) in systemic plasma concentration of cytokines including interleukine-6 (IL-6), tumor necrosis factor alpha (TNF- α), and C-reactive protein (CRP) (7). This low-grade inflammatory status has been found in CAD and PAD patients (15).

Evidence has shown that low-grade inflammation has highly been accepted as the basic condition in many diseases. For instance, low-grade inflammation is responsible for obesity and many obesity-related diseases such as type 2 diabetes, atherosclerosis, and metabolic syndrome. Furthermore, slight increase in level of CRP is associated with many none-inflammatory medical conditions (22). Most of these chronic diseases are associated with CAD and PAD. Therefore, underlying CAD and PAD risk factors could trigger endothelial dysfunction and inflammation.

A strong relationship between inflammation and atherothrombosis is demonstrated in CAD by the presence of macrophages, T-lymphocytes, and mast cells in unstable atherosclerotic plaques connected with the elevated expression of different inflammatory markers in plasma such as pro-inflammatory cytokines, amyloid A, adhesion molecules, and CRP (23).

Peripheral arterial disease (PAD)

PAD is defined as an arterial occlusive disease especially in lower limbs (24). PAD is another clinical manifestation of CAD with the same underlying pathophysiological process (25). Identifying sensitive markers for CAD diagnosis is the greatest goal of any cardiologist. PAD could be a sensitive marker for CAD and cerebrovascular disease (26).

Overall, 12–20% of general population aged between 55-65 years are affected by PAD (25). It is reported that 12 million people have atherosclerosis-associated conditions in United States (27,28). Moreover, about 27 million people suffer from PAD in Europe and USA (25,29).

According to the Table 1, Rutherford stage classification in PAD covers a wide range of symptoms and signs (30). Intermittent claudication also can induce pain or weakness and serious ischemia can induce ulcer, gangrene, or rest pain (24).

Table 1. Rutherford classification in PAD (30)

	0	if the patient is asymptomatic
Stage	1	if mild intermittent claudication is present
	2	if moderate intermittent claudication is present
	3	if severe intermittent claudication is present
	4	if ischemic rest pain is present
	5	if the patient has minor tissue loss
	6	if the patient has ulceration or gangrene

Same as CAD, smoking, hypertension, dyslipidemia, and diabetes mellitus (DM) are major risk factors of plaque progression in PAD (31). DM could increase the risk of PAD by two to four fold (32). In a study among German population, PAD had higher prevalence in DM patients versus non-diabetics (26.3%vs.15.3%) (33). In the USA, among 50 to 70 years old subjects, 22% of diabetic population had PAD, whereas PAD was diagnosed for around 21.1% of diabetic population in an Italian study on 30 years and older diabetic patients (34,35). Some novel biomarkers could increase in PAD such as C-reactive protein and homocysteine (36-38).

Most of the time superficial femoral, popliteal, abdominal aorta and iliac arteries are involved in peripheral atherosclerosis (24).

Some novel gene polymorphisms have been found in PAD such as SLC2A10, PAOD1, LSq-1, and CHRNA3 (rs1051730) (38). In 2010, SLC2A10 was found as an independent polymorphism gene that could lead diabetic patients to PAD (39). In recent studies, significant roles of genetic polymorphisms have been reported. Therefore, PAD is a genetics and environmental interaction disease with same risk factors of CAD.

Prevalence of peripheral arterial stenosis

In a study in USA, authors showed that around 5.8% of general population aged 40 years or more had peripheral arterial stenosis according to the ABI diagnostic test (40).

Weitz JI et al. reported that more than 27 million people suffered from PAD in Europe and north America (41). Diehm C. showed that PAD prevalence was around 15-20% of general population (42). Some scientists believe that CAD and PAD occur synchronized and more than 50% of the CAD positive patients could have active progressive plaque in peripheral arteries (43).

Diagnosis of PAD

1-Noninvasive method of ankle brachial index (ABI) is widely used for PAD detection, normal range between 0.9-1.2, the result that is less than 0.9 has 95% sensitivity and 99% specificity in disease diagnosis compared to PAD angiographic studies (44). According to Criqui MH et al, ABI more than 1.4 may be associated with cardiovascular events, thus both high and low ABI are unfavorable (45).

Some other diagnostic methods:

- 1-Contrast Angiography
- 2-Computed Tomographic Angiography
- 3-Magnetic Resonance Angiography
- 4-Doppler Ultrasonography
- 5-Pulse Volume Recording (31,41,46)

Treatment of Peripheral arterial stenosis

PAD treatments are divided into pharmacotherapy, Endovascular interventions, and surgical management (47). The most beneficial treatment of PAD is lifestyle changes and physical rehabilitation programmes (48).

Angiotensin-converting enzyme (ACE) inhibitors, statins, aspirin, pentoxifylline, cilostazol, naftidrofuryl, and ticlopidine are effective for medical management of PAD (47,49).

Judkins in 1964 performed the first endovascular intervention for treating PAD (46). endovascular intervention could be balloon angioplasty or stenting (46). In a study after 4 years follow-up, no significant difference found between surgical bypass and endovascular intervention (50).

Surgical management is seldom indicated in patients with PAD, as the patient at the risk of amputation (46).

Conclusion

In conclusion, cardiologists and general practitioners should consider PAD in a patient with CAD or DM as a strong correlated disease.

ABI, duplex sonography and some other non-invasive techniques are recommended for PAD diagnosis in the patients with the history of atherosclerosis. In addition, lifestyle changes in the PAD patients and pharmacotherapy should be considered.

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Conflict of Interest

The authors declare no conflict of interest.

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