Medical management of risk factors for vascular disease

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Abstract

Peripheral arterial disease (PAD) is a powerful marker of the risk of cardiovascular events such as stroke and myocardial infarction, even in asymptomatic patients. The development of PAD is underpinned by both modifiable risk factors, including smoking, diabetes, dyslipidaemia, hypertension and obesity and non-modifiable risk factors, including male gender and increased age. Optimizing medical management of risk factors, with tight control of diabetes, antiplatelet therapy and exercise, can significantly reduce risk of cardiovascular morbidity and mortality.

Keywords Cardiovascular risk factors; peripheral arterial disease; risk factor reduction

Background

Atherosclerosis is an inflammatory condition that can affect the arteries anywhere in the body, causing narrowing or blockage. Atherosclerosis below the level of the renal arteries, affecting the legs is known as peripheral arterial disease (PAD). PAD is common and is an indicator of widespread atherosclerosis in other vascular territories, such as the coronary, cerebral and carotid arteries, which in turn confer higher mortality rates.

In many patients, PAD begins as an asymptomatic condition, with the first manifestation being pain in the leg on walking which resolves with rest, intermittent claudication. If blood supply to the leg becomes further reduced to a level where pain is experienced at rest, and ulceration and gangrene occur, the leg is at risk of critical limb ischaemia (CLI).

In the Edinburgh Artery Study,[1] 4.5% of men and women over 55 years of age had intermittent claudication but a further 25% had evidence of asymptomatic disease. In one-third of the asymptomatic group, evidence of major vessel occlusion was found. Findings from the same population showed the annual risk of limb amputations to be less than 1–2%. Although the incidence of PAD varies widely depending on the population studied, it is thought to affect around 10% of people over 55.

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In the Edinburgh Artery Study,[1] 5–10% of subjects suffered a cardiovascular event such as heart attack or stroke. Although patients with asymptomatic PAD have increased cardiovascular risk, severity of PAD correlates with the level of cardiovascular risk. Ankle brachial pressure indices (ABPIs) are used to diagnose PAD, and are considered good predictors of cardiovascular morbidity and mortality. Meta-analyses have shown a low ABPI ($\leq$0.90) increases cardiovascular mortality, approximately doubling 10-year total mortality in these patients.

The major focus of treatment of PAD has shifted to prevention, addressing cardiovascular risk in patients, by optimizing medical management to prevent cardiovascular events.

Risk factors in patients with PAD

Cardiovascular (CV) risk factors may be modifiable, such as smoking, dyslipidaemia, hypertension and obesity or non-modifiable, such as age or male gender (Figure 1). Co-existing disease such as diabetes, chronic renal failure or coronary artery disease further increases the risk of cardiovascular events. Early detection of PAD allows CV risk factor modification.

Smoking

Smoking is the leading cause of preventable death in the Western world and the single most important risk factor for developing PAD, with amount and duration of tobacco use directly associated with development and progression of PAD. It is widely accepted that smoking cessation reduces the risk of adverse cardiovascular events and limb loss for patients with PAD. Both nicotine and carbon monoxide in cigarette smoke cause harm in a number of ways. Smoking increases blood pressure and serum cholesterol, reduces oxygen carriage, increases vascular resistance and vasospasm, and adversely affects vascular endothelium, platelets and coagulation systems.

Counselling and group therapy are known to increase smoking cessation success rates, and are best used in conjunction with pharmacotherapy, which now includes nicotine replacement, bupropion and varenicline. Varenicline is a partial nicotinic acetylcholine receptor agonist that works by stimulating dopamine release from the brain, resulting in relief of nicotine withdrawal symptoms and cigarette craving. Varenicline has been now recommended by the National Institute for Health and Care Excellence (NICE), in combination with counselling, for patients who wish to give up smoking.

In 2017, NICE released a surveillance report of their smoking guidelines, highlighting an increasing body of evidence supporting the use of electronic cigarettes for harm reduction. However, further evidence, including longer-term safety profiling of electronic cigarettes, is required.

Dyslipidaemias

Derangements of lipid metabolism and transport are strongly associated with CV risk in patients with PAD. The two main circulating lipids are cholesterol (important for cell membrane development and function, steroid hormone and bile acid synthesis) and triglycerides (important in energy metabolism). Cholesterol and triglyceride are transported in the blood as lipoproteins. Lipoproteins are complex molecules consisting of the triglyceride and cholesterol ester surrounded by phospholipids

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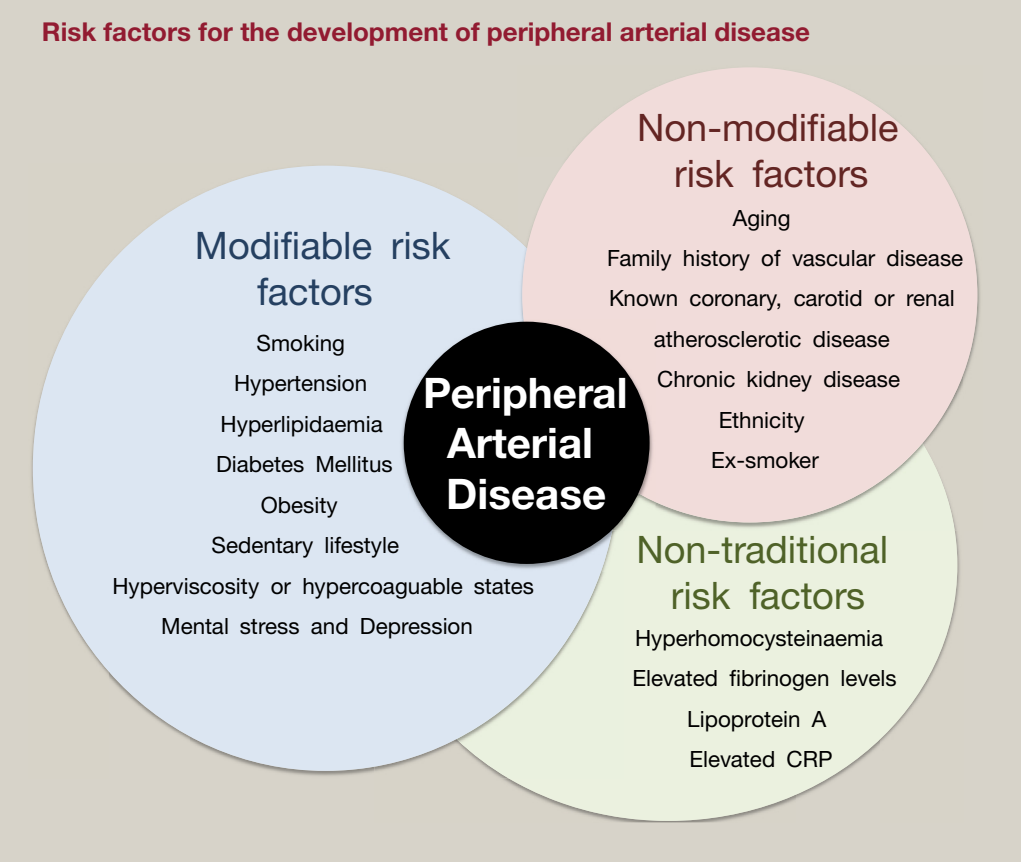

Figure 1

and cholesterol, with surface apolipoproteins that regulate lipoprotein metabolism. There are five types of lipoproteins, classified by density (chylomicrons; very low density, VLDL; intermediate density, IDL; low density, LDL; and high density, HDL).

After absorption from the small bowel, cholesterol is esterified and fatty acids combine with glycerol to form triglycerides. Esterified cholesterol and triglycerides are transported as chylomicrons in the circulation. Triglycerides may be released as free fatty acids and used as an energy source or stored in adipose tissue. The chylomicron remnant is taken up by the liver and cholesterol and triglyceride are transported around the body by other lipoproteins. Cholesterol is largely transported as HDL and LDL. LDL may release cholesterol to the liver for steroid hormone and bile acid synthesis or for incorporation into cell membranes. Circulating LDL that is not taken up may be incorporated into macrophages in the blood vessel wall, contributing to the development and progression of atherosclerosis (Figure 2). Circulating HDL can remove intracellular cholesterol and increased levels are associated with reduced cardiovascular risk.

Multiple epidemiological and observational cohort studies have shown a strong association between serum cholesterol levels, development of atherosclerosis and cardiovascular mortality. It has also been shown that there are further independent associations between PAD and LDL cholesterol, increased LDL: HDL ratios and circulating levels of apolipoproteins A and B.[2]

Cholesterol production in the liver is controlled by 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, which can be inhibited by statins, resulting in reduced LDL. As diet only achieves approximately 10% reduction in LDL, statins have become the main treatment for lowering cholesterol levels. Each 1 mmol/L reduction in LDL cholesterol results in approximately one-third reduction in mortality from coronary heart disease, independent of age, blood pressure and initial cholesterol concentration.[2]

In the Heart Protection Study,[3] 20,536 high-risk patients with cholesterol >3.5 mmol/L, 6748 of whom had PAD, were randomized to treatment with 40 mg simvastatin daily or placebo. In the PAD subgroup, simvastatin use was associated with a substantial reduction in cardiovascular events (24.7% versus 30.5% in the placebo group) during the 5-year follow-up. Similarly in CLI, the effect of statin therapy has been evaluated in a recent retrospective study.[4] This found patients that underwent first-time revascularization that were taking the recommended intensity of statin therapy had lower mortality rates and lower major adverse limb event rate over a median 380-day follow-up.

Based on the Heart Protection Study,[3] all patients with PAD should be given advice about dietary reduction of saturated fat and offered a statin. Statin therapy is recommended by NICE for all patients with PAD, starting with 20 mg atorvastatin for primary prevention and 80 mg atorvastatin for secondary prevention. Statins are generally well tolerated, with good patient compliance. Adverse side effects include derangement of liver enzymes and myositis. Statin therapy has also been associated with a slightly increased risk of developing diabetes, but the risk is low both in absolute terms and when compared with the reduction in coronary events. For those who are intolerant of

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