Minireview Article

Diet and its Relationship with Peripheral Vascular Disease

Abstract

Peripheral artery disease is a major health problem. It affects over 200 million people globally. It results in considerable suffering, curtailed functionality, and markedly reduced quality of life. Its presence prognosticates significantly higher major cardiovascular events. Atherosclerosis is the main disease process underlying its development and progression. Several lifestyle modifications have been shown to stem atherosclerosis. Consumption of a prudent diet is one such beneficial lifestyle. A prudent diet promotes the consumption of fruit, vegetables, whole grains, legumes, healthy fats such as nuts and seeds, low-fat dairy products, fish, and small amounts of lean meat. It limits the consumption of processed red meats, saturated fats, refined carbohydrates, and sugar-sweetened drinks. This manuscript reviews the present understanding of the role of diet in the development and progression of peripheral artery disease.

Keywords: prudent diet, fruits and vegetables, whole grains, processed red meat, saturated fat, peripheral vascular disease

Introduction

Peripheral arterial disease (PAD) affecting the lower extremities is a common clinical condition[1]. It is estimated to affect more than 200 million people globally[2]. While it affects only 4.3% in subjects ≥40 years, its prevalence rises to 14.5% in those over 70 years[3]. Since humans are living longer and the aging population is growing, the incidence and prevalence of PAD is on the rise[4]. It is diagnosed by the presence of an ankle-brachial index (ABI) of <0.9[5]. This noninvasive method is extremely reliable and has been validated against the gold standard - contrast angiography[6]. Fowkes reported that ABI had a sensitivity of 95% and a specificity of 100%[6]. Common risk factors for PAD, besides aging, include smoking, hypertension (HTN), diabetes mellitus (T2DM), dyslipidemia, and chronic renal failure[7]. It is estimated that the 1.5-fold increase in the incidence of PAD with one risk factor climbs to a 10-fold increase if there are three or more risk factors involved[8]. Smoking is a major risk factor and data indicates that more than 80% of patients with PAD are current or former smokers[9]. The underlying pathology is predominantly atherosclerosis[10]. Atherosclerosis is a progressive pathology and usually concurrently affects other parts of the vascular system, such as the coronary arteries and the carotid arteries[11]. Its pathophysiology includes low-grade inflammation, lipid accumulation, and plaque formation, leading to narrowing of the arteries[12]. In the legs this results in ischemia, causing pain on walking and a significant functional loss[13]. The disease may progress to non-healing leg wounds, gangrene, and ultimately result in limb amputation[14]. Besides the gradual progression seen in most patients, about 25% develop sudden onset of pain at rest due to acute limb ischemia, often requiring urgent surgical intervention[15]. The health-related quality of life is markedly reduced in these patients[16]. Treatment is usually pharmacological or surgical[17]. Concurrent supervised physical exercise helps reduce morbidity and mortality and leads to a

significant improvement in the health-related quality of life[18]. Overall mortality rates are high, and in patients with symptomatic disease, they approach 8.4% over 2 years[19]. Kochar et al. determined that in PAD patients, cardiovascular causes were responsible for the majority of deaths[20]. The economic burden (direct and indirect costs) related to PAD are extremely high[21]. Lifestyle factors, including diet, can play an important role in both primary and secondary prevention of this vascular disease[22].

Discussion

Peripheral artery disease is an atherosclerotic vascular disease, especially affecting the lower legs[1]. Since coronary artery disease (CAD) is also an atherosclerotic process, CAD and PAD share several common risk factors such as smoking, dyslipidemia, hypertension (HTN), and diabetes mellitus (T2DM)[23]. An unhealthy diet is also a major risk factor[24]. In a prospective cohort study, with a median follow-up of 21.7 years, Kulezic et al. reported an inverse association between adherence to a healthy diet and incident PAD[25]. A diet rich in processed red meat, saturated fats, refined carbohydrates, and low in micronutrients like magnesium, phosphorus, and calcium as well as vitamins A, D, or E and the vitamin B group, is pro-atherogenic[26,27]. A plant-based diet rich in fruits, vegetables, whole grains, and nuts helps reduce oxidative stress and endothelial dysfunction, and improve erythrocyte deformability, blood viscosity, oxygen perfusion, and is anti-atherosclerosis[28]. A prudent diet can therefore play a major role in both the primary (development) and secondary (progression) prevention of PAD[29].

Obesity

Diet plays an important role in obesity[30]. Obesity is usually determined by calculating the body mass index (BMI). A BMI ideally should be 18.5 kg/m² to 24.9 kg/m². A BMI of 25 kg/m² to 29,9 kg/m² is considered overweight. A BMI at or >30 kg/m² is designated as obese[31]. Compared to the BMI calculated obesity, abdominal obesity is more harmful to the cardiovascular system[32]. Abdominal obesity is objectively ascertained by several anthropometric measurements, such as the waist circumference (WC), waist-hip ratio and the waist height ratio[33]. WC should ideally be <102 cm in males and <88 cm in females when measured to the nearest 0.1 cm at the umbilical level in a standing position[34]. The waist-hip ratio is normally 0.85 or less for women and 0.9 or less for men[35]. The waist-height ratio is infrequently used – this is calculated by dividing the WC by the patients height. A ratio > 0.5 is consistent with central obesity[36]. Central or visceral obesity may exist even if the BMI is normal[37]. Several studies have linked abdominal obesity with PAD[38]. Wisse found that individuals with central or abdominal obesity had a 4-fold risk of developing PAD (Odds Ratio=4.532)[39]. Visceral fat is metabolically active and is associated with the development of insulin resistance, inflammation, and oxidative stress[40]. The result is an increase in atherosclerosis and PAD[41]. Abdominal obesity is also a known risk factor for CHD and this association has clinical significance as coronary heart disease (CHD) is responsible for many deaths in PAD patients[20]. Brouwer et al. reported that the presence of abdominal obesity was associated with a 61% increase in the risk of concomitant CHD in these patients[42]. Diet plays an important role in the prevention of excess body weight[30]. Although caloric intake restriction helps in weight reduction, the addition of exercise not only results in a greater weight loss but also helps to maintain the weight loss[43]. Weight loss is associated with an improvement

in several atherosclerosis risk biomarkers such as total cholesterol, low-density lipoprotein cholesterol, triglycerides, systolic and diastolic blood pressure, glucose, insulin, and C-reactive protein[44-48]. Consequently, weight loss in obese patients results in an improvement in peripheral artery disease[49].

Fruits and Vegetables

It is well known that high consumption of fruits and vegetables is associated with a lower risk of cardiovascular diseases, especially coronary artery disease and stroke[50]. Atherosclerosis is the common underlying pathology in these diseases – and PAD[23]. Hung in 2003 found a modest beneficial effect on PAD, with fruit and vegetable consumption, in a study of male health professionals during a 12-year follow-up[51]. A Mediterranean dietary pattern (rich in plant-based foods and polyphenol-rich olive oil) is associated with a 56% reduced risk of PAD[52]. In a recent cross-sectional study involving over 3.6 million individuals, Heffron et al. found that the odds of PAD were reduced by 18% when individuals consuming 3 or more servings of fruits and vegetables per day were compared to those consuming >3 servings of fruits and vegetables less than once a month[53]. In a recent study, Chen et al., in a study of 138,506 US postmenopausal women (1993–1998) in the Women's Health Initiative, with no known PAD at baseline, reported that higher intakes of vegetable protein were associated with a lower risk of developing PAD[54]. Phytochemicals in plants are postulated to exert vascular benefits in these patients[55].

Whole grains/Fiber/legumes/Nuts

Whole-grain consumption was not found to be associated with reduced risk of PAD in a prospective cohort study of 14,082 individuals in the US with a mean follow-up of 19.9 years[56]. However, whole grains are an important source of dietary fiber, and most studies on fiber intake have shown that fiber consumption beneficially influences PAD[57]. In a cross-sectional study (1,267 subjects aged > or =30 years), lower consumption of fiber from whole grains was found in individuals with PAD[57]. Dietary fiber exerts a protective effect on PAD via several mechanisms. These include reducing obesity, lowering cholesterol, increasing insulin sensitivity, reducing serum glucose levels, producing short-chain fatty acids by gut bacteria, and reducing inflammation[58,59]. It has also been noted that individuals with a higher intake of fiber often lead healthier lifestyles, including participating in physical activity and avoiding tobacco smoking. Legume and nut intake is also helpful. In the recent study by Chen et al., higher intakes of legumes and dietary fiber were associated with a lower risk of PAD[60]. In a study of adults, Heffron et al. found that increased nut intake was inversely associated with PAD prevalence[61]. Inflammation is strongly associated with atherosclerosis and nuts decrease inflammation. In the Multi-Ethnic Study of Atherosclerosis (MESA) (nearly 6000 participants), consumption of nuts and seeds was inversely associated with levels of inflammatory markers such as C-reactive protein, interleukin-6, and fibrinogen[62].

Coffee/tea/Chocolate

Light-to-moderate coffee intake (0.5-3 cups/day) has been shown to be cardioprotective[63,64]. Coffee consumption is associated with a decreased risk of developing PAD[65]. In the Atherosclerosis Risk in Communities (ARIC) Study, the authors reported an inverse association

between coffee intake and incident PAD[56]. In a retrospective analysis of 237 women (45-54 years of age), 16.8% of women that drank more than five cups/day of coffee had an ABI lower than 0.9 and as compared to its presence in 27.4% of women who were non-drinkers[65]. Green tea consumption also provides beneficial vascular effects – in a study of 12 healthy men (29 ± 6 yrs), drinking catechin-rich green tea prevented abnormalities of vascular function induced by unhealthy lifestyles[66]. Both coffee and tea (green or black) are high in the beneficial polyphenol antioxidants[67,68]. Cocoa is also PAD friendly. Dark chocolate improves maximal walking distance and maximal walking time, 2 hours after ingestion in PAD patients[69]. No benefits were noted with milk chocolate. Dark chocolate is richer in polyphenol compared to milk chocolate[70]. As noted with tea and coffee, the polyphenols help in improving endothelial function by reducing oxidative stress and increasing nitric oxide generation[67,68,71]. As a result, atherosclerosis is retarded.

Alcohol

As noted in coronary artery disease, the risk of PAD is beneficially affected by low to moderate alcohol consumption. In the Cardiovascular Health Study, of older adults (5635 participants) alcohol consumption of 1-13 drinks per week was associated with a lower risk of PAD[72]. In the ARIC (Atherosclerosis Risk in Communities) Study of 14,082 participants, 1–6 drinks/wk, but not ≥7 drinks, was associated with a lower risk of incident PAD[65]. The benefits are postulated to be partly due to an improved lipid profile (especially a higher HDL-cholesterol) and better insulin sensitivity[73,74].

Red Meat

Red meat intake, especially that of processed red meat, has been repeatedly shown to increase the risk of cardiovascular diseases (CVD)[75-77]. A detrimental association with PAD has also been noted[25,65]. In a recent study, Chen et al. reported that intake of unprocessed red meat, processed meat, and regular soft drinks was associated with a higher risk of PAD[60]. High levels of sodium and nitrate preservatives in processed meats raise blood pressure and increase the incidence of T2DM, both contributing to the increased incidence of PAD[78-80].

Saturated and Unsaturated Fat

The deleterious role of saturated fats on atherosclerotic vascular disease is well known[81]. In 2008, in a cross-sectional study of 1,267 subjects (aged > or =30 years) individuals with PAD had a higher intake of total (72.8 vs 69.1 g, p=0.016) and saturated fatty acids (17.4 vs 16.3 g, p=0.012)[82]. This harmful relationship was confirmed by Naqvi et al[83]. In their study of 6352 adults aged 40 years and older participating in the U.S. National Health and Nutrition Examination Survey between 1999 and 2004, the intake of saturated fatty acids was associated with a higher prevalence of PAD (adjusted odds ratio 1.30). Mazidi et al. reported higher plasma trans-fatty acid levels in PAD patients, compared to those without the disease[84]. On the other hand, a higher intake of unsaturated fats, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) appear to be beneficial[85,86]. Dark fish is a major source of EPA and DHA[87]. However, in a recent cohort of 14,082 participants followed for a mean of 19.9 years, the authors found no association between consumption of fish and the risk of incident PAD[56].

Another recent study involving 55,248 participants (a median of 13.6 years of follow-up), Cox regression analyses with adjustments for established risk factors showed no statistically significant associations between intake of EPA, DHA, or EPA + DHA and the rate of incident PAD[88]. However, recent data from the Danish Diet, Cancer and Health cohort pf 3204 participants provided contrary results. The authors found a statistically significant lower rate of PAD in the highest quintile of EPA (hazard ratio [HR]: 0.55) consumption and a nonsignificant lower rate for DHA (HR: 0.79) consumption. They also reported that a high content of marine n-3 polyunsaturated fatty acids (PUFAs) in adipose tissue, in particular EPA, was associated with a lower risk of incident PAD[89]. This is in line with previous observations that marine n-3 PUFAs protect against atherosclerotic diseases in other beds. such as the coronaries (myocardial infarction)[90] and the carotid and cerebral arteries (ischemic stroke)[91]. Supplementation with omega-3 fatty acids does not improve hemodynamic or clinical outcomes in PAD patients[92]. The data on the benefits of marine unsaturated fatty acids on PAD is therefore unclear.

Vitamins/Micronutrients

PAD has an inverse relationship with vitamin A[93], vitamin C[94], vitamin D[95], vitamin E[96], and folic acid[97] intake. International studies have documented deficiency of these vitamins in PAD. In the USA, it was found that vitamin A was low in 57%, vitamin C in 33%, and vitamin E in 100% of patients with PAD[98]. In a study done in Australia, it was found that among PAD patients 16.7% were deficient in vitamin A, 78.1% in vitamin C, 0% in vitamin E, 58.1% in vitamin D, and 50% in iron and zinc[99]. In another study, individuals without PAD had higher plasma vitamins concentrations compared with PAD patients[84]. Several studies have shown a vascular benefit (improved endothelial function) in patients with atherosclerosis with supplementation with vitamin C[100], vitamin E[101], and vitamin D[102]. Clinical benefit with oral supplementation of these vitamins in a pill form has however not shown any persuasive clinical benefit[103]. On the other hand, a dietary intake of foods high in these vitamins (and iron and zinc) is associated with a decreased prevalence of PAD[84,93,104]. Eating a variety of food items usually provides a complex combination of nutrients, and this may result in beneficial interactions leading to a decrease in atherosclerotic vascular disease (as compared to supplementation with individual micronutrients).

Special Diets

In the PREDIMED (Primary Prevention of Cardiovascular Disease with a Mediterranean Diet) randomized clinical trial, individuals randomly assigned to the Mediterranean diet (MedD) demonstrated a significantly lower rate of incident PAD when compared to those in the low-fat diet group[105]. In a recent systemic review of 82 studies (30% RCT) Adegbola et al. found that the MedD was associated with a lower incidence of PAD[106]. In the Framingham Heart Study, HTN increased the risk of intermittent claudication several fold.[107]. Hypertension is common in PAD patients[108]. Dash diet is effective in reducing HTN and should therefore lead to a reduction in PAD[109]. A vegetarian diet is typically higher in fiber, antioxidants, phytochemicals, and plant protein and lower in saturated fat compared to non-vegetarian dietary patterns[110]. A plant-based diet has significant health benefits, and studies have shown that a plant-based diet can be an effective treatment for obesity[111], T2DM[112], HTN[113], hyperlipidemia[114], and heart disease[115]. A

vegetarian diet helps in preventing or slowing the development of atherosclerosis in several ways. There is prevention of vascular endothelial cell injury, LDL-cholesterol oxidation, and macrophage activation[116]. Vegetarians have less atherosclerosis, and this should help decrease the incidence of PAD in this population.

Conclusion

Dietary intervention is an inexpensive way to combat the ever-increasing burden of PAD. Peripheral artery disease is associated with increased risk of major cardiovascular events, limb amputation, and overall mortality. As a vascular disease, it is relatively common and highly indicative of atherosclerotic disease in the coronary and the cerebral circulation. It has been noted repeatedly that low consumption of saturated fat, foods of animal origin and salt, and increased intake of plant-based foods such as whole grains, fruits, vegetables, legumes, and nuts, are linked with reduced atherosclerosis risk[117]. This finding has also been noted in patients with PAD[25]. In conclusion, there is ample evidence-based data supporting the consumption of a plant based prudent diet for the primary and secondary prevention of PAD.

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