

## Role of Diet and Exercise Management of Peripheral Artery Disease: Review of Literatures

**Manal Abdulaziz Murad<sup>1\*</sup>, Fahad Saleh Alsefry<sup>2</sup>, Feras Loay Alkindi<sup>3</sup>, Saud Saad Mannaa Alamri<sup>4</sup>, Abdulrahman Saud Abdulrahman Alasmari<sup>4</sup>, Salman Hudayhid Alqurashi<sup>5</sup>, Hassan Muwafak Habis<sup>6</sup>, Ali Ibrahim Ali Albayh<sup>6</sup>, Abdulaziz Saud Abdulrahman Alasmari<sup>7</sup>, Ibrahim Ahmed Ibrahim Asseri<sup>4</sup>, Saleh Omar Bajahlan<sup>8</sup> and Fawaz Abdulkreem Alzhrani<sup>9</sup>**

<sup>1</sup>Assistant Professor and Consultant Family Medicine, Family Medicine Department, Faculty of Medicine, King Abdulaziz University, Saudi Arabia

<sup>2</sup>Al Laith General Hospital, Saudi Arabia

<sup>3</sup>King Fahad General Hospital Jeddah, Saudi Arabia

<sup>4</sup>King Khalid University, Saudi Arabia

<sup>5</sup>King Faisal Specialist Hospital Jeddah, Saudi Arabia

<sup>6</sup>King Abdulaziz Hospital Makkah, Saudi Arabia

<sup>7</sup>Armed Forces Hospital- Najran, Saudi Arabia

<sup>8</sup>Alshara'e 7 Primary Health Care Center, Saudi Arabia

<sup>9</sup>Health Sciences College at Al-Ieth, Saudi Arabia

**\*Corresponding Author:** Manal Abdulaziz Murad, Assistant Professor and Consultant Family Medicine, Family Medicine Department, Faculty of Medicine, King Abdulaziz University, Saudi Arabia.

**Received:** May 18, 2019; **Published:** June 21, 2019

### Abstract

**Introduction:** Peripheral arterial disease (PAD) is an important life-threatening or limb-threatening disease that affects about six percent of the United States general population aged about forty years, roughly sixteen million and a half American individuals. Prevention and management of Peripheral arterial disease has focused on the alteration of cardiovascular predisposing factors, that include tobacco smoking, elevated blood pressure, diabetes mellitus, and increase lipids levels. Life-style improvements include protocols for smoking cessation, physical exercise programs, and changes in the diet. Pharmacological interventions include the management of this chronic condition with cholesterol-lowering drugs (like statins), anti-platelet drugs, and anti-hypertensive drugs, like angiotensin-converting enzyme inhibitors (ACEIs) and alpha-blocker agents. although these guidelines are available, Peripheral arterial disease patients are usually under-treated with regard to decreased predisposing factors when compared to patients with other heart diseases

**Aim of Work:** In this review, we will discuss Role of diet and exercise management of peripheral artery disease.

**Methodology:** We did a systematic search for Role of diet and exercise management of peripheral artery disease using PubMed search engine (<http://www.ncbi.nlm.nih.gov/>) and Google Scholar search engine (<https://scholar.google.com>). All relevant studies were retrieved and discussed. We only included full articles.

**Conclusions:** In our review we give solid evidence to the role of nutrition and physical exercise in the prevalence of peripheral artery disease. We conclude that in specific populations, anti-oxidants (like vitamin A, Vitamin C, and Vitamin E), B vitamins (including folate and B6), and fibers intake were found to be linked to a protective effect going beyond that explained by traditional cardiovascular risk factors. Additionally, a diet that is low in saturated fats and high in omega-3 fatty acids might also confer a beneficial effect against peripheral artery disease. Among more than sixteen million Americans who suffer from peripheral artery disease, our study demonstrated that extremely poor dietary habits, with average levels of nutritional intake far below what the FDA suggested dietary guidelines. This needs considerable dietary improvement on a nationwide scale.

**Keywords:** Diet; Exercise; Lifestyle; Peripheral Artery Disease; Management

### Introduction

Peripheral arterial disease (PAD) is an important life-threatening or limb-threatening disease that affects about six percent of the United States general population aged about forty years, roughly sixteen million and a half American individuals. Prevention and management of Peripheral arterial disease has focused on the alteration of cardiovascular predisposing factors, that include tobacco smoking, elevated blood pressure, diabetes mellitus, and increase lipids levels. Life-style improvements include protocols for smoking cessation, physical exercise programs, and changes in the diet. Pharmacological interventions include the management of this chronic condition with cholesterol-lowering drugs (like statins), anti-platelet drugs, and anti-hypertensive drugs, like angiotensin-converting enzyme inhibitors (ACEIs) and alpha-blocker agents [1]. Although these guidelines are available, Peripheral arterial disease patients are usually under-treated with regard to decreased predisposing factors when compared to patients with other heart diseases [2].

General dietary modifications usually include the use of a low-fat, low-salt diet for prevention of cardiovascular disease, but guidelines for the consumption of specific nutrients are still not present. The World Health Organization (WHO) Study Group 3 suggested protocols for the prevention of cardiovascular disease that include a diet that is low in total fat (about thirty percent of calories) and saturated fat (about ten percent of calories) and lacks trans-fatty (saturated) acids. Salt consumption must be decreased to about five grams per day (about 90 mmol/d). Consumption of a wide spectrum of fruits, vegetables, and whole grains (about 400 g/d) is recommended. On the other hand, no suggestions can be made regarding the intake of vitamins B, C, E and folic acid because of the absence of solid clinical evidence.

In this review, we will discuss the most recent evidence regarding Role of diet and exercise management of peripheral artery disease.

### Methodology

We did a systematic search for Role of diet and exercise management of peripheral artery disease using PubMed search engine (<http://www.ncbi.nlm.nih.gov/>) and Google Scholar search engine (<https://scholar.google.com>). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: diet, exercise, lifestyle, peripheral artery disease, management.

### Nutrition

There is an increasing evidence from experimental studies and clinical trials that the diet could potentially have a significant effect on the mechanisms of atherosclerosis. Diet does not only affect the concentrations of circulating blood lipids but can also alter the immune and inflammatory processes that is present in the epithelium that impacts the pathophysiology of atherosclerotic plaque [3]. This has caused a number of putative nutritional goals that might lead to protection or secondary intervention in patients with Peripheral arterial disease. On the other hand, many clinical trials have conflicting conclusions regarding different specific nutrient supplementations [4]. Dietetic protocols are often modified for overall cardiovascular diseases and do not particularly focus on peripheral arterial diseases [5].

A significant important finding of this study is the correlation between poor caloric intake and a higher risk of developing Peripheral arterial disease. Among individuals in the US who do not have Peripheral arterial disease, there is a significant elevation in the total amount of calories consumed and in all specific nutrient intakes, including saturated and polyunsaturated fatty acids. People with Peripheral arterial disease had reported reduced total calorie and nutrient intake and had a higher prevalence of comorbid diseases, including elevated blood pressure, coronary artery diseases, and diabetes mellitus. This trend towards poor caloric consumption in patients with Peripheral arterial disease and critical limb ischemia has been previously mentioned [6].

On the other hand, improved nutrition and freedom from Peripheral arterial disease has also been correlated. The Edinburgh Artery study assessed the effects of dietary factors on ABI in a previous trial of more than 1,500 individuals [7]. This demonstrated the presence of a correlation between having higher ABI and increased consumption of cereal fiber, meat, alcohol, and vitamins C and E. another study found a similar pattern of poor dietary habits and higher occurrence of Peripheral arterial disease. importantly, most American individu-

als do not meet the US Food and Drug Administration (FDA)-recommended intake of nutrients; this difference is more present among individuals who have Peripheral arterial disease. However, the association between nutrition and Peripheral arterial disease could be potentially confounded by the presence of other coexistent medical conditions, such as older age, diabetes mellitus, coronary artery disease and tobacco smoking.

### Antioxidants

Vitamin A (retinol) is a fat-soluble anti-oxidant that is essential for vision, the growth of bones, and the immune system. It is present in many orange and yellow vegetables, in addition to butter, eggs, and liver. Vitamin C (ascorbic acid), on the other hand, is a water-soluble anti-oxidant that is most commonly found in citrus fruit. Vitamin C is generally well-known for its effects on the prevention of scurvy along with its important value in the immune system functions and maintenance of the redox state. Previous clinical trials have demonstrated that vitamin C concentrations are decreased in patients with Peripheral arterial disease and this was also found to be associated with less walking distance and the development of systemic inflammatory reactions (C-reactive protein) [8]. On the other hand, not all clinical studies that involved vitamin C supplementations have demonstrated positive associations on Peripheral arterial disease [9]. Vitamin E (tocopherol) is another membrane-bound anti-oxidant that has been associated with decreased cellular damage in cardiovascular conditions. It is present mostly in nuts, vegetable oils, and fish. Vitamin E supplementation has been used for long time as a preventative measure for cardiovascular conditions. In the Rotterdam study, increased vitamin E consumption was associated with a decrease in Peripheral arterial disease and an increase in ABI. On the other hand, in another large, randomized trial (the HOPE trial) [10], dietary supplementations with vitamin E demonstrated no significant reductions in cardiovascular diseases among individuals who had diabetes mellitus or vascular conditions.

This strong correlation that is observed in the US general population between improved anti-oxidant intake and reduced Peripheral arterial disease must not be mis-interpreted as a cause-and-effect association. More solid evidence for the use of anti-oxidants must be provided by larger trials, like the Critical Leg Ischemia Prevention Study (CLIPS), which assesses both vitamin C and E supplementation.

### Folate and other B vitamins

Hyperhomocysteinemia is known to be an important independent predisposing factor for the development of Peripheral arterial disease. About thirty percent of patients with Peripheral arterial disease have been found to have hyperhomocysteinemia, and the severity of their disease is significantly associated with plasma homocysteine concentrations [11]. Folate supplementations have been found to decrease plasma homocysteine concentrations in Peripheral arterial disease patients [12] and the addition of vitamins B6 and B12 might increase this impact. Additionally, several observational studies have demonstrated a strong association between B vitamin consumption and protection from Peripheral arterial disease. Folate and vitamin B6 consumption are important predictors of Peripheral arterial disease in males who are aged about fifty years, regardless of other cardiovascular risk factors [13]. The Health Professionals Follow-up Study also demonstrated a strong relationship between folate and B6 consumption and Peripheral arterial disease risk. As a matter of fact, a previous meta-analysis proposed that decreasing homocysteine concentrations in patients with cardiovascular conditions by about 3 mol/L could potentially decrease the risk of cardiac events by sixteen percent. The results of randomized studies have not, however, been as encouraging. In the HOPE trial, high-risk cardiovascular individuals were randomized to receive treatment with combination therapy (vitamin B6, folate and B12) or placebo. Despite the presence of significant declines in homocysteine concentrations, there was no observed decline in the overall cardiovascular diseases. Additionally, in the Norwegian Vitamin Trial (NORVIT) [14], showed that B vitamins supplementation did actually increase the risk of developing cardiac diseases. It must be kept in mind that these trials were all particularly designed to assess cardiac outcomes, and Peripheral arterial disease end points were not specifically assessed.

### Fiber

There is a huge amount of observational studies that provided evidence for the possible beneficial roles of fibers in the diet. The Edinburgh Artery study demonstrated the presence of a positive correlation between cereal fiber consumption and elevated ABI findings. A similar positive correlation was found between cereal fiber consumption and elevated ABI the Health Professional's Follow-up Study. Additionally, some authors suggest that elevated fibers intake might exert anti-inflammatory processes. In a previous study that used the 1999 to 2000 NHANES data, a strong correlation was found between fibers consumption and C-reactive protein concentrations. Randomized

studies that provide solid evidence for fiber consumption and the development of Peripheral arterial disease are not present. generally, it is challenging to isolate the particular effects of fibers consumption. This is because of that Food, like cereal, that has a high of fiber is also includes high concentrations of other nutrients, like folate and vitamin E.

### Exercise

Lack of Physical activity is an essential predisposing factor for the development of obesity and other cardiovascular conditions. Vascular endothelial dysfunction is a key event in the development of CVD and is associated with a sedentary lifestyle in otherwise healthy individuals. additionally, vascular endothelial dysfunction might be worsened in individuals with sedentary life who are overweight and/or resistant to insulin, since increased body fat is linked to increased concentrations of pro-atherogenic inflammatory adipokines and cytokines that decrease the nitric oxide levels (NO) and other upstream paracrine signaling transmitters that decrease vascular health. Since blood flow related shear stress is a significant stimulus to the release of NO from the endothelial tissue, disturbed blood flow is a likely mechanism for vascular endothelial dysfunction. Evidence demonstrates that normal routine exercise can have important effects on developing cardiovascular diseases and the predisposing factors that improve peripheral arterial function and health. Both aerobic and anaerobic physical exercise are usually thought to benefit endothelial function and are often recommended for cardiovascular health, including the treatment of increased weight, elevated blood pressure, and resistance against insulin. On the other hand, many other possible factors like age, disease status, and ethnicity appear to possibly impact these outcomes. Despite that evidence that supports the effects of exercise is compelling, the ideal prescription (intensity and volume) and the exact mechanism underlying the effects of physical exercise on arterial functioning and cardiometabolic risk still needs to be detected. The focus of this review is on the evidence supporting exercise interventions for peripheral arterial function.

### Mechanisms mediating endothelium-dependent vasodilation in the peripheral circulation

Normal Vascular endothelial function indicates a variety of physiologic processes which re related to the maintenance of vascular wall proper homeostasis, namely the integrity of the endothelial tissue. The synthesis of NO transmitter by the vascular endothelium is specifically essential in the regulation of blood vessels. Endothelium-derived NO is produced from the guanidine-nitrogen terminal of L-arginine by the effects of the enzyme that is called endothelial nitric oxide synthase (eNOS) after stimulation by receptor-dependent agonists (like acetylcholine/ACh) or receptor-independent stimuli like elevated flow through vessels or shear stress. In the context of blood flow-induced shear stress, increased cytosolic calcium ( $Ca^{2+}$ ) stimulates the activation of the eNOS enzyme to catalyze the conversion of L-arginine to L-citrulline and NO, with tetra-hydrobiopterin and NADPH as important cofactors [15]. NO then diffuses into near smooth muscle cells to stimulate the soluble enzyme guanylate cyclase to synthesize cGMP4. This stimulating reaction finally lead the smooth muscle cells to relax and this consequently leads to a state of vasodilation. Physiologic dysfunction of endothelium-dependent vasodilation could cause deleterious changes in the blood flow during any physiologic stress (including physical exercise, states of hypoxia, and bleeding) and leads to increases in blood pressure and the development of cardiovascular abnormalities.

Decreased physiological responsiveness to endothelium-dependent vasodilator stimuli indicates the underlying presence of endothelial dysfunction and is usually a result of the absence of balance between vasodilator and vasoconstrictor molecules synthesized by the endothelial tissue. There is solid evidence showing that the most important characteristic of endothelial dysfunction is a decreased in endothelium-derived NO bioavailability [16]. Despite that the exact mechanism by which this decline happens might be based on the disease type, severity and the presence of cardiovascular predisposing factors.

On the other hand, the more likely physiological mechanisms include: the presence of disturbances in the NO stimulating pathways; decreased bioavailability of L-arginine and/or BH4; altered expression and functional activity of eNOS; extracellular scavenging of NO by reactive oxygen species (ROS); and elevated synthesis of endothelium-derived vasoconstrictors.

**Sedentary lifestyles, obesity, and arterial function**

The term “sedentary lifestyle” is generally used on people who do not practice any regular physical exercise or those who do not achieve the least recommendations for physical activity, which are thirty minutes of any kind of physical activity on most week days. More specific exercise recommendations were published by the American College of Sports Medicine (ACSM) and the American Heart Association (AHA) suggested the practice of twenty to thirty minutes of moderate- to severe aerobic physical exercise, 3 to 5 days every week. Around the world, inactivity status is considered to be a major cause of death that can be prevented and an important independent predisposing factor for the development of cardiovascular diseases and a wide spectrum of other chronic illnesses like elevated blood pressure, diabetes mellitus type 2 along with some specific types of malignancies [17]. Decreased physical activity has been found to be linked to decreased normal endothelial function, which is considered to be an important early marker that predicts atherosclerosis propensity.

Impaired normal endothelial physiological function presents a pathophysiologic mechanism that links sedentary lifestyle to cardiovascular risk. As an example, elevated body mass index in individuals with normal or mildly ill coronary arteries was independently linked to decreased coronary dilation to intraarterial infusions of ACh when compared to otherwise normal healthy patients who have normal BMIs. The exact mechanisms of this pathological dysfunction in obese individuals is still not well-understood. Plasma inflammatory biomarkers like interleukin-6, c-reactive protein, endothelin-1, and tumor necrosis factor-alpha are increased in obese patients and synthesized by different cell types, like activated adipocytes, leukocytes, and endothelial cells [18]. This data indicates that the pro-inflammatory environment caused by obesity might play an important role in the development of coronary and systemic vascular dysfunctions.

Adipose tissue is considered to be a metabolically active organ and an important resource of pro-inflammatory particles and cytokines. Leptin is a known adipokine that is elevated in obese individuals and play an important role in ROS mediated endothelial dysfunctions in endothelial tissue during the gain of weight [26]. Leptin could signal C-RP synthesis in endothelial tissues and this reaction seems to involve oxidative stress. The particular association between leptin and vascular ROS during obesity and the mechanism of physical exercise in altering this reaction has not been yet completely understood. One of the previous studies demonstrated that circulating leptin is decreased among adults who are performing resistance physical exercise and linked to improved conduit artery endothelial function during the loss of weight.

**Role of exercise on arterial function in health**

Solid evidence suggests that most bouts of physical exercise improve NO bioavailability and decrease oxidative stress through up-regulation of endogenous vasodilators and increased anti-oxidant capacity in small and large blood vessels. The impact of physical exercise on the arterial function without the presence of cardiovascular and cardiovascular predisposing factors have been less studied since endothelial physiological functions tend to be usually well maintained in this group of patients [19].

Our understanding of the blood vessels regulation of blood flow and blood perfusion within the peripheral circulation has improved significantly within the past thirty years. It is clear that the endothelial tissue has an essential role in regulating the functions of the blood vessels and that arterial stiffness a crucial indicator that predicts arterial function. Alterations in arterial function are critical in the pathogenesis of obesity and the cardiometabolic phenotype associated with obesity (i.e. HTN and insulin resistance). The studies reviewed above highlight the contributing role of vascular dysfunction in exacerbating insulin resistance-associated reduction in NO availability. The impact of this outcome may contribute to increase peripheral vascular resistance, impairment of insulin delivery to tissues resulting in poor glucose disposal. Importantly, ET is an important non-pharmacologic intervention that has been found to reverse and restore endothelial function in patients with cardiometabolic disease. The mechanisms of action of the effects of this lifestyle intervention are multifactorial and include effects at the level of the endothelial cell, smooth muscle and several upstream signaling mechanisms (i.e. insulin and ET-1). Future research will need to focus on the optimal mode, intensity, and duration of ET prescription in diverse populations for improving arterial fun

## Conclusions

In our review we give solid evidence to the role of nutrition and physical exercise in the prevalence of peripheral artery disease. We conclude that in specific populations, anti-oxidants (like vitamin A, Vitamin C, and Vitamin E), B vitamins (including folate and B6), and fibers intake were found to be linked to a protective effect going beyond that explained by traditional cardiovascular risk factors. Additionally, a diet that is low in saturated fats and high in omega-3 fatty acids might also confer a beneficial effect against peripheral artery disease. Among more than sixteen million Americans who suffer from peripheral artery disease, our study demonstrated that extremely poor dietary habits, with average levels of nutritional intake far below what the FDA suggested dietary guidelines. This needs considerable dietary improvement on a nationwide scale.

## Bibliography

1. Hankey GJ, *et al.* "Medical treatment of peripheral arterial disease". *Journal of the American Medical Association* 295.5 (2006): 547-553.
2. McDermott MM, *et al.* "Atherosclerotic risk factors are less intensively treated in patients with peripheral arterial disease than in patients with coronary artery disease". *Journal of General Internal Medicine* 12.4 (1997): 209-215.
3. Ross R. "Atherosclerosis—an inflammatory disease". *New England Journal of Medicine* 340.2 (1999): 115-126.
4. Carrero JJ and Grimble RF. "Does nutrition have a role in peripheral vascular disease?" *British Journal of Nutrition* 95.2 (2006): 217-229.
5. Mead A, *et al.* "Dietetic guidelines on food and nutrition in the secondary prevention of cardiovascular disease - evidence from systematic reviews of randomized controlled trials (second update, January 2006)". *Journal of Human Nutrition and Dietetics* 19.6 (2006): 401-419.
6. Spark JL, *et al.* "Patients with chronic critical limb ischaemia have reduced total antioxidant capacity and impaired nutritional status". *European Journal of Vascular and Endovascular Surgery* 24.6 (2002): 535-539.
7. Donnan PT, *et al.* "Diet as a risk factor for peripheral arterial disease in the general population: the Edinburgh Artery Study". *American Journal of Clinical Nutrition* 57.6 (1993): 917-921.
8. Langlois M, *et al.* "Serum vitamin C concentration is low in peripheral arterial disease and is associated with inflammation and severity of atherosclerosis". *Circulation* 103.14 (2001): 1863-1868.
9. Podmore ID, *et al.* "Vitamin C exhibits pro-oxidant properties". *Nature* 392.6676 (1998): 559.
10. Lonn E, *et al.* "Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial". *Journal of the American Medical Association* 293.11 (2005): 1338-1347.
11. Ciccarone E, *et al.* "Homocysteine levels are associated with the severity of peripheral arterial disease in type 2 diabetic patients". *Journal of Thrombosis and Haemostasis* 1.12 (2003): 2540-2547.
12. van den Berg M, *et al.* "Combined vitamin B6 plus folic acid therapy in young patients with arteriosclerosis and hyperhomocysteinemia". *Journal of Vascular Surgery* 20.6 (1994): 933-940.
13. Wilmink AB, *et al.* "Dietary folate and vitamin B6 are independent predictors of peripheral arterial occlusive disease". *Journal of Vascular Surgery* 39.3 (2004): 513-516.

14. Bønaa KH., *et al.* "Homocysteine lowering and cardiovascular events after acute myocardial infarction". *New England Journal of Medicine* 354.15 (2006): 1578-1588.
15. Powell KE., *et al.* "Physical activity and the incidence of coronary heart disease". *Annual Review of Public Health* 8 (1987): 253-287.
16. Lteif A., *et al.* "Endothelin limits insulin action in obese/insulin resistant humans". *Diabetes* 56.3 (2007): 728-734.
17. Peake J and Suzuki K. "Neutrophil activation, antioxidant supplements and exercise-induced oxidative stress". *Exercise Immunology Review* 10 (2004): 129-141.
18. Fantuzzi G and Mazzone T. "Adipose tissue and atherosclerosis: Exploring the connection". *Arteriosclerosis, Thrombosis, and Vascular Biology* 27.5 (2007): 996-1003.
19. Phillips SA., *et al.* "Resistance and aerobic exercise protects against acute endothelial impairment induced by a single exposure to hypertension during exertion". *Journal of Applied Physiology* 110.4 (2011): 1013-1020.

**Volume 15 Issue 7 July 2019**

**©All rights reserved by Manal Abdulaziz Murad., *et al.***