Peripheral artery disease (PAD) affects 3%-10% of the Western population and if remains untreated can have devastating consequences to patients and their families. This review article analyzes how healthy dietary habits can decrease PAD rates when applied in the general population. The aim is to focus on dietary, nutritional and weight management interventions in patients with established PAD. Most adults with PAD are overweight or obese, while three out of four patients are characterized by deficiencies in vitamins and minerals (Thomas et al., 2019). Both suboptimal nutritional status and high fat mass have been associated with worsening of the ambulatory status and vascular health in patients with PAD and claudication (Gardner et al., 2011). Nutritional advice and weight management are of paramount significance in PAD management (Hirsch et al., 2001).

Primary prevention with emphasis on healthy nutritional habits may be advantageous in terms of decreasing rates of PAD, whereas a secondary prevention approach can be useful in slowing PAD progression and improving claudication symptoms (Unkart et al., 2019).

Pre-existence of coronary or cerebrovascular atherosclerosis, hypertension, diabetes mellitus, smoking, population minorities and advancing age, are all associated with PAD (Fowkes et al., 2013; Joosten et al., 2012; Selvin and Erlinger, 2004). PAD ranges from asymptomatic to symptomatic, while among multiple classifications, the Rutherford classification is the most commonly used to categorize PAD patients according to their symptoms. Asymptomatic PAD is defined as Rutherford Stage 0, while patients presenting with mild or moderate claudication, or walking-induced leg muscle pain relieved by rest, are classified as Stages 1 and 2, respectively. In later stages of PAD, patients exhibit foot pain at rest (Stage 4), and/or ulcers and gangrene (Stages 5 and 6) (Anderson et al., 2013; Hossain et al., 2019; Kullo and Rooke, 2016).
American Heart Association (AHA) recommends ankle brachial index as the initial diagnostic test for PAD (Alahdab et al., 2015). The Edinburgh Artery Study showed that only 15% of patients with ankle brachial index ≤ 0.90 - which is diagnostic for the disease - experience intermittent claudication, whereas almost 35% reported no symptoms (Campia et al., 2019). Farah et al. showed that the walking capacity of 133 patients with PAD fluctuated according to their comorbidities, with diabetes and coronary artery disease being independent predictors of their ambulatory status (Farah et al., 2013). Untreated or inadequately treated PAD may lead to critical limb ischemia (CLI) or even amputation (Leng et al., 1994). CLI is characterized by chronic (≥ 2 weeks) ischemic rest pain, non-healing wounds/ulcers, or gangrene in one or both legs, attributable to proven arterial occlusive disease (Kokkinidis et al., 2020c). A small percentage of patients with PAD, will develop finally CLI and will have much higher risk for amputation and mortality compared to claudicants. It is striking that the one-year risk of limb loss is 30% and the five-year all-cause mortality is 50% in patients with CLI (Kokkinidis and Armstrong, 2020; Kokkinidis et al., 2020b; Norgren et al., 2007). Coronary artery disease and PAD share a common pathogenesis and risk factors for development (e.g., smoking, dyslipidemia, hypertension, and diabetes mellitus) (Bhatt et al., 2006). Plaque rupture or erosion can provoke superimposed atherothrombosis and subsequent vessel occlusion, leading to cardiovascular (CV) events, including myocardial infarction (MI), stroke, limb ischemia, and CV death (Bauersachs and Zannad, 2018). Thus, prognosis can be improved through secondary prevention measures, with lifestyle changes, medicinal control of modifiable CV risk factors, and the prevention of blood clot formation with antithrombotic therapies (Cortés-Beringola et al., 2017). The purpose of this review is to present the current evidence regarding the association between healthy nutrition, weight management and specific targeted nutritional habits with PAD risk, progression, and outcomes.

2. Role of nutrition and dietary habits in prevention of peripheral artery disease and other atherosclerotic cardiovascular diseases

Atherosclerosis is characterized by chronic systemic low-grade vascular inflammation (Hansson and Hermansson, 2011). Accumulation of lipids and inflammatory cytokines damage the vascular endothelium, provoking the atherosclerotic plaque formation (Insull, 2009). Metabolic disorders and unfavorable lipid profiles have been found to promote atherogenesis by increasing oxidized low-density lipoprotein (oxLDL) (Badimon et al., 2009). Although emphasis is given mainly on reducing LDL-cholesterol (LDL-C) -by the restriction of saturated fat, trans-fat and cholesterol- there are also other beneficial dietary complements that could slow down the atherosclerosis progress (Torres et al., 2015). A recent study tried to demonstrate the main determinants of diet quality showing that being male, having low income, living with other people, physical inactivity, and current smoking were generally the main factors associated with a diet low in fruits, vegetables, legumes, wholegrains as well as nuts and seeds (Mauger et al., 2020). The Global Burden of Disease (GBD) Study analyzed the relationship between single dietary risk factors and cardiovascular diseases (CVDs) (Meier et al., 2019).

According to the GBD more than 9.1 million deaths from CVDs worldwide are attributable to dietary risks (Global Burden of Disease Cancer et al., 2019). Therefore, optimized dietary patterns might assist to overcome the burden of CVDs. In terms of food and nutrient groups, five risk factors had an attributable fraction greater than 10% of the total diet-related CVD burden: diet low in whole grains (20.4%), diet low in nuts and seeds (16.2%), diet low in fruits (12.5%), diet high in sodium (12.0%), and diet low in seafood omega-3 PUFA (10.8%) (Meier et al., 2019).

The dietary intake of polyunsaturated fatty acids (PUFA) is vital, as they cannot be synthesized in vivo. The main sources of PUFA are fatty fish (herring/mackerel and salmon/whitefish/char), flax seeds and nuts -omega-3- as well as vegetable oils (safflower oil, peanut butter, avocado oil etc.) and animal fat -omega-6- (Wall et al., 2010). Omega-3 PUFAs regulate blood pressure and the thrombosis response. They are involved in inhibiting eicosanoids production and result to blunted arterial wall inflammatory response (Wall et al., 2010). The American Heart Association (AHA) recommends a weekly intake of ≥ 200 mg omega-3 (2 portions/week of fatty fish or oral omega-3 supplements) (Rimm et al., 2018). Controversy exists in the literature regarding the role of n-6 fatty acids in CVD prevention. A diet containing an excess of 10% n-6 fatty acids has been evoked to induce adverse effects against CVD, mostly due to their proinflammatory and oxidation effects (Patterson et al., 2012). It is suggested that dietary n-6 fatty acids may increase oxidation susceptibility of LDL-C and VLDL-C (Hammad et al., 2016; Russo, 2009). High intake of n-6 PUFA might also be associated with increased vasospasm, vasocostriction, and blood viscosity (Hammad et al., 2016). However, not all omega-6 PUFA have negative effect in the progression of the disease, and AHA recommends lower consumption of anti-atherogenic omega-6 PUFA, such as dihomo-γ-linolenic acid (DGLA), which can be metabolized to prostaglandin E1 (Das, 2008). Butyrate is a short-chain fatty acid which is produced by the fermentation of fibers from the gut microbiota in intestine. Studies on mice fed with 1% butyrate showed that it can reduce the pro-inflammatory cytokines (IL-1β, IL-6, and TNF) and nitric oxide production in small and stable atherosclerotic lesions (Aguiar et al., 2014; Menzel et al., 2004).

Plant-based diets have been associated with potential benefits in cardiovascular health. Phytosterols, steroids of similar structure with cholesterol, are associated with lower plasma LDL-C levels, achieved via altering the expression of ABCA1 (upregulation) (Andersson et al., 2004; Katan et al., 2003). A consumption of 2 g/daily of phytosterols and flavonoids is recommended (Sabeva et al., 2011). Fruits and vegetables are the main sources of flavonoids, with catechin (present in green tea and cocoa) being the main representative of the cluster (Falcone Ferreyra et al., 2012). They can reduce the production of pro-inflammatory cytokines and chemokines by the vascular endothelial cells. Similarly, hydrogen sulphide (H₂S), a derivative of allicin -a secondary garlic metabolite-, can reduce the leukocytes adherence in the arterial wall and the formation of foam cells (Yamakuchi et al., 2008).

Recent large cohort studies support that Mediterranean Diet is effective both in primary and secondary prevention of cardiovascular events (Martínez-González et al., 2015; Ruiz-Canela and Martínez-González, 2014). This is probably achieved via oxida-
tive stress reduction. Numerous polyphenol compounds in olive oil exert anti-inflammatory effects, including oleuropein, tyrosol, and hydroxytyrosol (Martinez-Gonzalez et al., 2018; Massaro et al., 2010). The EUROLIVE study revealed that the consumption of virgin olive oil can reduce oxidative stress and triacylglycerols levels while increasing the levels of high-density lipoprotein (HDL)-cholesterol in serum plasma (Covas et al., 2006).

Among vitamins, vitamin E and C as well as supplementation with potassium, zinc and magnesium have been shown to have a cardioprotective role. The underlying protective mechanism is based on oxidative stress reduction, stabilizing in this way the atherosclerotic plaque and regulating the fluctuation of blood pressure (Ashor et al., 2014; Homarbaksh and Schachter, 2009; Villacorta et al., 2003). Folate and vitamin B (B2, B6, B12) can decrease homocysteine levels which has been linked to increased proliferation of vascular smooth muscle cells and collagen synthesis (Hustad et al., 2000). Homocysteine is additionally interfering with the vascular integrity via induction of endothelial dysfunction and reduction of arterial wall elasticity (Hustad et al., 2000; Lin et al., 2012).

PAD prevalence was higher in patients who consumed greater amounts of saturated fats, meat, and animal products. On the contrary, foods rich in fiber, such as cereal fiber, as well as antioxidants (vitamins A, C, E) and polyunsaturated fats have a protective role in PAD (Fontana, 2018; Nosova et al., 2015). Down-regulation of vitamin B6, B12 and folate acid levels - all of each involved in homeostasis of homocysteine - could increase PAD risk (Fenton et al., 2016). More specifically, the conversion of homocysteine to cystathionine -derivative of homocysteine- is vitamin B6-dependent, whereas re-methylation requires the co-factors folate and vitamin B12 (Blom and Smulders, 2011). Folate deficiency might contribute to a decreased ability to maintain homocysteine homeostasis and potentially lead to a toxic accumulation of unmetabolized homocysteine in the serum (Booth et al., 2004). This deficiency is associated with endothelial dysfunction, vasoconstriction, and endovascular inflammation (Dionisio et al., 2010).

3. Diets

3.1 Mediterranean diet

Mediterranean Diet has been associated with lower rates of PAD and improvement of claudication symptoms (Ruiz-Canela and Martinez-Gonzalez, 2014). Mediterranean diet is characterized by generous amounts of olive oil as the main culinary fat and is characterized by high consumption of plant-derived foods (fruit, vegetables, legumes, nuts and seeds, and whole grain cereals); frequent, but moderate intake of - mainly red - wine with meals; moderate consumption of seafood and dairy products (especially yogurt and cheese, but not whole milk, butter or cream), poultry and eggs; and low consumption of sweet desserts, red and processed meat (Ruiz-Canela and Martinez-Gonzalez, 2014). The PREDIMED study showed a significant relative risk reduction in type 2 diabetes mellitus (40%), PAD (64%) incidence and other cardiovascular complications (30%) in patients following a Mediterranean diet. Olive oil consumption seems to be superior to nuts oil in terms of cardiovascular outcomes (Martinez-Gonzalez et al., 2015; Ruiz-Canela and Martinez-Gonzalez, 2014). Dietary advice can be helpful for the prevention of PAD in diabetics, even in populations traditionally accustomed to Mediterranean dietary habits (Ciccarone et al., 2003). High adherence to this dietary pattern was not only associated with low prevalence of obesity and hypertension, but also decreased the odds of concentric left ventricle hypertrophy. Mediterranean diet was proved to increase ventricular filling, which in turn increased end-diastolic filling, left ventricular volumes, stroke volume, and ejection fraction (Mauger et al., 2019). Data from the Kardiozize Brno cohort showed that high adherence to the prudent dietary pattern was associated with lower odds of abdominal obesity, abnormal glucose concentration, and metabolic syndrome. This finding is of clinical impact in primary prevention for cardiovascular events (Levitan et al., 2016).

3.2 Plant based-vegetarian-vegan diets

Vegetarian diets are followed by more than 5% of the population and have been recognized as potentially cardio-protective (Delaney et al., 2019). Vegetarian diets emphasize the consumption of fruits, vegetables, nuts and grains with limitation of dairy or meat products (Delaney et al., 2019). Vegetarians are less prone to diabetes mellitus, hypertension, hypercholesterolemia and mortality from ischemic heart disease and stroke (Delaney et al., 2009). Given the low content of fat, cholesterol, salt and red meat, vegetarian diet may decrease vascular endothelial cell injury (Rathod et al., 2016). Polyphenols may decrease oxidation of LDL and prevent oxidized LDL (OxLDL)-induced monocyte adhesion to vascular endothelial, monocyte transformation into macrophages, and foam cell formation. Reducing red meat intake may decrease trimethylamine-N-oxide (TMAO) formation (Salomon du Mont et al., 2017). Decreasing TMAO formation inhibits atherogenesis by down-regulating macrophage uptake of OxLDL (Tuso et al., 2015). The Vegan diet has become more popular recently but its benefit on cardiovascular outcomes is still debated, given the negative effect on the vascular epithelium (Ruiz-Canela and Martinez-Gonzalez, 2014; Wischmeyer et al., 2018).

3.3 Ketogenic diet

Ketogenic diet is based on a reduction in carbohydrates (usually less than 50 g/day) and a relative increase in the proportions of proteins and fats (Ciccarone et al., 2003). A stricter version is the very-low-carbohydrate ketogenic diet, where carbohydrates are limited to less than 30 g/day (Ciccarone et al., 2003). The inadequate glucose storage leads to ketones bodies production to cover the energy needs of central nervous system (Veech, 2004). A recent meta-analysis showed that ketogenic diet is associated with reduction of body mass index (BMI), abdominal circumference, both systolic and diastolic blood pressure, triglycerides levels, fasting plasma glucose and HbA1c; and increase in HDL- cholesterol levels (Rathod et al., 2016). Nonetheless, no significant benefit was reported on the prevention of cardiovascular events in the follow-up (Naude et al., 2014). Adverse events of ketogenic diet include but are not limited to kidney stones, osteoporosis, and impaired growth (Bueno et al., 2013).

3.4 Intermittent fasting diet

In a recent statement AHA analyzed the intermittent fasting program benefits in cardiovascular health (Tinsley and Horne, 2018). Intermittent fasting program is based on alternate-day (ADF) or periodic fasting (PF) for weight loss. Benefits include reductions in total cholesterol (-6 to 21%), LDL cholesterol (-7
to 32%) and triglycerides (-16 to 42%) as well as systolic blood pressure (3 to 8%) and diastolic blood pressure (6 to 10%) (Tinsley and Horne, 2018). Furthermore, a weight reduction of 3-8% over a course of 3-24 weeks has been reported to decrease the risk of type 2 diabetes and the production of atherosclerotic inflammatory cytokines (Tinsley and Horne, 2018). The potential mechanisms associated with these beneficial effects include improved insulin sensitivity, increased levels of fibroblast growth factor 21, reduced inflammation and oxidative stress, and enhanced cellular and molecular adaptive stress responses. It is difficult to understand whether fasting directly affects cardiovascular markers or its benefits depend on weight loss (Mattson et al., 2014; Plamavila et al., 2013). On the other hand, it can be associated with frequent fractures due to osteoporosis in elderly patients (Dardano et al., 2014). The caloric restriction often leads to reactive hypoglycemia which is detrimental for patients using diabetic medications. A study in 2018, analyzed the way that frequency and timing of meals may affect cardiovascular health outcomes (Agodi et al., 2018). It is suggested that skipping breakfast or the afternoon snack may adversely affect the circadian clock and correlates with increased postprandial glycemic response, triglycerides level and total cholesterol/HDL-C ratio. These are risk factors for poor cardiovascular health, while higher eating time interval and frequency may promote a more ideal cardiovascular profile (Agodi et al., 2018). More data are needed in terms of overall safety and cardiovascular risk reduction of patients who follow an intermittent fasting program (Malinowski et al., 2019) (Table S1).

4. Importance of dietary habits and nutrition in patients with established peripheral artery disease

Dietary habits are a cornerstone in the development and progression of PAD (Hirsch et al., 2001). Combined nutrition and exercise interventions reduce walking impairment compared to patients practicing exercise alone (Fahrleitner et al., 2002; Wang et al., 2008). During the last decade, multiple interactions between medications used for medical management of PAD and dietary constituents have been reported. Deficiencies such as Q10 Coenzyme- which supplementation can be cardioprotective-, zinc, and vitamin B12 interact with lipid lowering medications, antihypertensive drugs and oral hypoglycemic agents, respectively (Booth et al., 2004; Fenton et al., 2016). Similarly, increased levels of vitamins K and E, with parallel administration of warfarin as anticoagulation therapy for PAD’s comorbidities, have been associated with vascular calcification. Thus, patients on coumadin should be routinely monitored for these nutrient deficiencies and at the same time evaluated for candidacy for newer oral anticoagulants (Foley et al., 2017; Kokkinidis et al., 2020a; Siasos et al., 2020). Novel oral anticoagulants in combination with aspirin may provide an alternative treatment in PAD, however, it is deemed necessary to identify patient subgroups who will benefit the most (Koutsoumpelis et al., 2018). Hypovitaminosis D has been associated with higher prevalence and severity of PAD disease. The potential mechanism is explained by the fact that hyperparathyroidism increases the risk of osteomalacia and arterial calcification (Krishna, 2019). Folate and vitamin D deficiencies have been linked to an increased risk of PAD and worsening ambulatory status (Kokkinidis et al., 2020a). The Institute of Medicine’s Food and Nutrition Board recommends consumption of 700 IU/day of vitamin D, 400 µg/day folate, 1.7 mg/day vitamin B6, 2.4 µg/day vitamin B12 and a daily maximum of 1250 mg sodium in patients with PAD (Nosova et al., 2015) (Table 1).

CLI is characterized by significantly increased levels of atherosclerotic inflammatory cytokines when compared to intermittent claudication (Jalkanen et al., 2016). CLI has a 25% risk of mortality and 30% of major limb amputation within 12 months from its diagnosis (Kokkinidis and Armstrong, 2017; Norgren et al., 2007). Patients with CLI often present with ulcers and muscle atrophy (Kinlay, 2016). Ischemic ulceration exacerbates protein loss which is estimated to be as high as 100 g per day (Russell, 2001). Thus a correction of 10% is recommended to the estimated energy requirements in patients with CLI (Harris-Benedict equation) (Cereda et al., 2011). Deficiencies of vitamin A, vitamin C, vitamin D and E as well as zinc and selenium have been all found to have negative effects on wound healing, given that when present, they all augment the healing process (Chua et al., 2011; Mirastschijski et al., 2013). Patients with malnutrition and CLI have the highest mortality risk in the first 30 days post amputation (Delaney et al., 2019). Patients with ischemic ulceration or rest pain often undergo revascularization to avoid amputation (Salomon du Mont et al., 2017). Due to the catabolic state occurring after limb loss, post-amputation patients have even higher increase in the energy levels requirements. Appropriate supplementation of energy, protein and micronutrients is essential (Wischmeyer et al., 2018). The systemic nature of the disease is prevalent and its manifestations seem to vary. The incidence of renal artery stenosis is increased in patients with PAD. This diagnosis must therefore be kept in mind when hypertension resistant to medical therapy is encountered in these patients. The optimal blood pressure for patients with PAD without diabetes mellitus is 140/90 and 130/80 for patients with diabetes or chronic kidney disease (Singer and Kite, 2008). Upper extremity artery disease due to atherosclerosis is mostly situated at the level of the brachiocephalic trunk and the subclavian and axillary arteries (Aboyans et al., 2007). While the vast majority of strokes presented secondary to carotid and vertebral artery disease than cardioembolism (Donnan et al., 1998).

5. Weight changes and atherosclerotic cardiovascular disease

The AHA recently established the concept of the AHA Life’s Simple 7 (LS7) metrics based on four healthy behaviors (non-smoking, normal weight, moderate physical activity, and a healthy diet) and three health factors (normal cholesterol, blood pressure, and fasting blood glucose) (Ogumoroti et al., 2018). Weight status constitutes a significant role in the progression of atherosclerotic disease (Neeland et al., 2019). Overweight status and obesity are characterised by excessive expansion of white adipose tissue (WAT) mass (Lempesis et al., 2020). The pathophysiology of obesity and its complications, however, is not only driven by the increase in WAT mass, but mainly by the dysfunctional status of the organ, also known as adiposopathy (Blüher, 2013; Goossens, 2008, 2017; Goossens and Blaak, 2015; Lempesis et al., 2020). Adiposopathy is comprised by adipocyte hypertrophy, decreased adipose tissue blood flow, altered oxygen levels within the tis-
sue, a state of chronic low-grade inflammation and blunted lipid metabolism (Frayn and Karpe, 2014; Goossens and Blaak, 2015; Shulman, 2014). The later includes impaired capacity to store the surplus of dietary lipids, resulting to deposition of ectopic fat - fat accumulating in body locations where it is not physiologically stored, like liver and muscle-, and a shift to visceral adipose tissue (fat storage in the intraperitoneal and retroperitoneal spaces), contributing to increased circulating free fatty acids, oxidative stress, systematic inflammation, adipokine dysregulation and insulin resistance (Bays, 2012; Frayn and Karpe, 2014; Goossens and Blaak, 2013; Lempesis et al., 2020; Shulman, 2014). Thus, presence or absence of adiposopathy can partially explain the heterogeneity of obesity and its manifestations, through modulation of risk factors such as diabetes mellitus, hypertension and dyslipidemia (Bays et al., 2008).

Weight loss should be recommended for all obese and overweight patients. The initial goal is 5% to 10% weight reduction in the first 6 months (Jensen et al., 2014). The Diabetes Prevention Program study randomized 3,234 patients in three clusters: 1) Intensive lifestyle intervention (ILI) group, 2) metformin group and 3) placebo group. The mean weight loss after a 2.8 years' follow-up was 5.6, 2.1 and 0.1, respectively. The first and the second group had a reduction of the incidence of diabetes by 58% and 18%, compared to placebo (Diabetes Prevention Program Research Group, 2009; Knowler et al., 2002). Similarly, the Look AHEAD trial presented that ILI patients had a greater reduction in glycosylated hemoglobin (HgA1c) and a more favorable blood pressure and lipid profile (Gadde et al., 2018). Weight loss achieved with diet and exercise improves cardiometabolic risk factors, reduces the incidence of diabetes, dyslipidemia, and achieves glycemic and blood pressure control (Look AHEAD Research Group et al., 2013). In conclusion, weight management effectively reduces the atherosclerosis progression via downregulating risk factors such as diabetes mellitus, hyperlipidemia, hypertension and adiposopathy (Gadde et al., 2018).

### 6. Weight changes and peripheral artery disease

The current gold-standard intervention to improve walking performance in patients with intermittent claudication is supervised exercise, followed by active monitoring of nutrition status (Kokkinidis et al., 2019). Targeting weight loss has been associated with less decline in 6-minutes-walk test (Tinsley and Horne, 2018). Polonsky et al. showed that compared to patients with weight gain, patients with intentional weight loss > 5 pounds had less annual decline in 6-minutes-walk distance, despite losing greater muscle calf area (Polonsky et al., 2019). A meta-analysis of 3 weight-loss trials based on calorie restriction with physical activity showed that every 1-kg loss of fat mass predicted a 0.01-m/s increase in walking speed, independently of losing lean mass (Beavers et al., 2013). The potential mechanism is the exacerbation of a low grade inflammatory response triggered by the increased visceral fat around skeletal muscles and the genetic downregulation of mitochondrial gene leading to dysfunction (Sparks et al., 2005; Tzoulaki et al., 2005). Thus, emphasizing weight reduction in early stages of the disease decreases mortality rates and improves the quality of life, avoiding the detrimental effects of sarcopenia in later stages (Kokkinidis et al., 2019).

---

**Table 1. Diet and lifestyle recommendations for Peripheral Artery Disease prevention.**

| Fats | Proteins | Trace & Elements | Fruits, Vegetables & Anti-Oxidants |
|------|----------|------------------|-----------------------------------|
| - Saturated fats to < 7% of daily caloric intake. | - Adjust requirement if hypermetabolic state. | - Vitamin D = 700 IU/day | - Five serves of vegetables, two serves of fruit, four serves of whole grain per day. |
| - Increase the consumption of omega-3 fatty acids. | - Variable adjustment depending on presence/size of ulceration/per-operative state (magnitude of surgery performed)/active infection. | - Folate acid = 400 μg/day | - Consume whole grain in preference to white or refined grain products. |
| - At least two fish meals per week. | - Olive oil for cooking. | | - Tobacco use. |
| - High unsaturated fat content and the antioxidant hydroxytyrosol. | - Consume low-fat dairy products. | | - Avoid |
| - Limit red meat to one meal per week. | - Replace with beans or legumes. | | - 1–2 cups of green tea daily. |
| | | | - Regular physical activity. |
| | | | - Minimum of 30 min moderate intensity physical activity at least 5 days/week. |

Table 1. Diet and lifestyle recommendations for Peripheral Artery Disease prevention.
The obesity paradox is based on observations of overweight and obese patients with established PAD, who had better prognosis compared to their non-overweight/non-obese peers (Miller et al., 2012; Palaiodimos et al., 2020). This may be explained by the fact that a significant percentage of the overweight elderly patients, suffered from frailty and sarcopenia. Sarcopenia is defined as an unintentional loss of lean muscle mass, frequently associated with aging. Sarcopenic-lean and sarcopenic-obese patients are two distinct sarcopenia groups. Preservation of muscle mass in collaboration with myokines and circulating hormones influence the progression of PAD (Addison et al., 2018). Almost 25% of patients with intermittent claudication have sarcopenia and those patients tend to have a worse walking performance compared to their non-sarcopenic peers (Kokkinidis et al., 2019). The obesity paradox has potential implications on CLI as well. Higher BMI is associated with lower rates of mortality in patients with lower extremities ulcers (Kinlay, 2016). On the other hand, obese patients with CLI often belong to the subtype of sarcopenic-obesity, suffering from both muscle atrophy and obesity related complications (Tzoulaki et al., 2005). Sarcopenia increases platelet dysfunction, promoting hypercoagulable states and impairs wound healing by the expression of atherosclerotic cytokines (Hicks et al., 2018; Sugai et al., 2018). Sarcopenia has been associated with higher rates of incomplete wound healing, amputation, major adverse cardiovascular events, major adverse limb events and mortality (Kokkinidis et al., 2020d; Miller et al., 2012). Timely wound healing is of utmost importance as far the outcome of the procedure is concerned (Chi et al., 2019; Wischmeyer et al., 2018).

7. Conclusion and future perspectives

Patients with PAD and CLI are nutritionally vulnerable groups and subsequently, nutritional support, emphasis on proper diet and close monitoring of weight are prerequisites for optimal outcomes. Population level interventions can decrease the prevalence of PAD, while at the same time, early aggressive medical management with emphasis on the aforementioned in patients with PAD, can likely improve the pain free walking distance, quality of life, survival, while decreasing functional decline, amputation and overall mortality rates in these individuals. FOURIER trial showed that low-dose antithrombotic therapy with aspirin and lipid lowering -with a PCSK9 inhibitor- are associated with reduction of both cardiovascular and limb adverse events (Bonaca et al., 2018). Furthermore, analyses of HOPE trial have demonstrated that using statins and ACE-Is reduce cardiovascular risk in patients with PAD, with less clear effects with antiplatelet therapies. Implementation of these therapies remains challenging because of the cost and the burden of polypharmacy. Further studies are necessary to identify the patients with PAD who will benefit the most from these advances (Heart Outcomes Prevention Evaluation Study Investigators et al., 2000). While further research attempts are anticipated, emphasis on proper nutrition, dietary interventions and weight management should be part of the PAD multidisciplinary team (primary care physicians, cardiologists, endocrinologists, nutritionists and dieticians, podiatrists and vascular interventionists) that participates in the care of those patients.

Authors’ Contributions
All authors contributed to conception, design, and writing of the manuscript.

Acknowledgments
The authors declare no funding, no contribution from other persons.

Conflict of Interest
Carlos Mena: Consultant for Abbott, Boston Sci, COOK, Medtronic, Cardinal Health and Optum Labs.

Supplementary material
Supplementary material associated with this article can be found in the online version, at https://rcm.impress.com/EN/10.31083/j.rcm.2020.04.202.

Submitted: October 01, 2020
Revised: October 29, 2020
Accepted: November 03, 2020
Published: December 30, 2020

References
Aboyans, V., Criqui, M. H., McDermott, M. M., Allison, M. A., Denerberg, J. O., Shadman, R. and Fronck, A. (2007) The vital prognosis of subclavian stenosis. Journal of the American College of Cardiology 49, 1540-1545.
Addison, O., Prior, S. J., Kundi, R., Serra, M. C., Katzel, L. I., Gardner, A. W. and Ryan, A. S. (2018) Sarcopenia in peripheral arterial disease: Prevalence and effect on functional status. Archives of Physical Medicine and Rehabilitation 99, 623-628.
Agodi, A., Maugeri, A., Kunzova, S., Sochor, O., Bauerova, H., Kiacova, N., Barchitta, M. and Vinciguerra, M. (2018) Association of dietary patterns with metabolic syndrome: Results from the kardiovize brno 2030 study. Nutrients 10, 898.
Aguilar, E. C., Leonel, A. J., Teixeira, L. G., Silva, A. R., Silva, J. F., Peleazz, J. M., Capettini, L. S., Lemos, V. S., Santos, R. A. and Alvarez-Leite, J. I. (2014) Butyrate impairs atherogenesis by reducing plaque inflammation and vulnerability and decreasing nkappab activation. Nutrition, Metabolism, and Cardiovascular Diseases 24, 606-613.
Alahdab, F., Wang, A. T., Elratai, T. A., Malgor, R. D., Rizvi, A. Z., Lane, M. A., Prokop, L. J., Montori, V. M., Conte, M. S. and Murad, M. H. (2015) A systematic review for the screening for peripheral arterial disease in asymptomatic patients. Journal of Vascular Surgery 61, 42S-53S.
Anderson, J. L., Halperin, J. L., Albert, N. M., Bozkurt, B., Brindis, R. G., Curtis, L. H., DeMets, D., Guyton, R. A., Hochman, J. S., Kovacs, R. J., Ohman, E. M., Pressler, S. J., Selike, F. W. and Shen, W. K. (2013) Management of patients with peripheral artery disease (compilation of 2005 and 2011 Acclf(Aha guideline recommendations): A report of the american college of cardiology foundation/american heart association task force on practice guidelines. Circulation 127, 1425-1443.
Andersson, S. W., Skinner, J., Ellegard, L., Welch, A. A., Bingham, S., Mulligan, A., Andersson, H. and Khaw, K. T. (2004) Intake of dietary plant sterols is inversely related to serum cholesterol concentration in men and women in the epic norfolk population: A cross-sectional study. European Journal of Clinical Nutrition 58, 1378-1385.
Antonelli-Incalzi, R., Pedone, C., McDermott, M. M., Bandinelli, S., Miniati, B., Lova, R. M., Lauretani, F. and Ferrucci, L. (2006) Association between nutrient intake and peripheral artery disease: Results from the inchianti study. Atherosclerosis 186, 200-206.
Ashor, A. W., Lara, J., Mathers, J. C. and Siervo, M. (2014) Effect of vitamin C on endothelial function in health and disease: A systematic review and meta-analysis of randomised controlled trials. Atherosclerosis 235, 9-20.
Badimon, L., Vilahur, G. and Padro, T. (2009) Lipoproteins, platelets and atherothrombosis. Revista Española de Cardiología 62, 1161-1178.

Bausersch, R. and Zannad, F. (2018) Rivaroxaban: A new treatment paradigm in the setting of vascular protection? Thrombosis and Haemostasis 118, S12-S22.

Bays, H. E. (2011) Adipose tissue dysfunction: A cardiovascular disease? Journal of the American College of Cardiology 57, 2461-2473.

Bays, H. E. (2012) Adiposity pathology, diabetes mellitus, and primary prevention of atherosclerotic coronary artery disease: Treating "sick fat" through improving fat function with antiobesity therapies. The American Journal of Cardiology 110, 4B-12B.

Bays, H. E., Gonzalez-Campoy, J. M., Bray, G. A., Kitabchi, A. E., Bergman, D. A., Schorr, A. B., Rodbard, H. W. and Henry, R. R. (2008) Pathogenic potential of adipose tissue and metabolic consequences of adipocyte hypertrophy and increased visceral adiposity. Expert Review of Cardiovascular Therapy 6, 343-368.

Beavers, K. M., Miller, M. E., Rejeski, W. J., Nicklas, B. J. and Kritchevsky, S. B. (2013) Fat mass loss predicts gain in physical function with intentional weight loss in older adults. The Journals of Gerontology: Series A, Biological Sciences and Medical Sciences 68, 80-86.

Bhatt, D. L., Steg, P. G., Ohman, E. M., Hirsch, A. T., Ikeda, Y., Mas, J. L., Goto, S., Liau, C. S., Richardson, J. A., Rother, J., Wilson, P. W. and Investigators, R. R. (2006) International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. The Journal of the American Medical Association 295, 180-189.

Blom, H. J. and Smulders, Y. (2011) Overview of homocysteine and arterial thrombosis. Journal of Thrombosis and Haemostasis 9, 1111-1117.

Bueno, N. B., de Melo, I. S., de Oliveira, S. L. and da Rocha Ataide, T. (2013) Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: A meta-analysis of randomised controlled trials. British Journal of Nutrition 110, 1178-1187.

Campia, U., Gerhard-Herman, M., Piazza, G. and Goldhaber, S. Z. (2019) Peripheral artery disease: Past, present, and future. The American Journal of Medicine 132, 1133-1141.

Cereda, E., Klersy, C., Rondanelli, M. and Cacchialanza, R. (2011) Energy intake and vascular risk: A systematic review and meta-analysis of observational studies. Journal of the American Dietetic Association 111, 1868-1876.

Chi, W. K., Tan, G. and Yan, B. (2019) Prognostic nutritional index as a predictor of prognosis in patients with critical limb ischemia who underwent endovascular revascularization therapy. Journal of the American College of Cardiology 73, 2064.

Chua, G. T., Chan, Y. C. and Cheng, S. W. (2011) Vitamin D status and peripheral arterial disease: Evidence so far. Vascular health and Risk Management 7, 671-675.

Ciccareone, E., Di Castelnuovo, A., Salcuni, M., Siani, A., Giacco, A., Donati, M. B., De Gaetano, G., Capani, F., Iacoviello, L. and Gendiabe, I. (2003) A high-score mediterranean dietary pattern is associated with a reduced risk of peripheral arterial disease in Italian patients with type 2 diabetes. Journal of Thrombosis and Haemostasis 1, 1744-1752.

Conway, K., Dillon, M., Evans, J., Hovells-Jones, R., Price, P., Harding, K. and Hill, S. J. B. o. S. (2005) A double-blinded, randomised study to determine the effect of omega-3 marine triglycerides on intermittent Claudication. Yearbook 2005, The Vascular Society of Great Britain & Ireland.

Cortés-Beringola, A., Fitzsimons, D., Pelliccia, A., Moreno, G., Martín-Arroyo, R., Bueno, H., Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain and Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain (2017) Planning secondary prevention: Room for improvement. European Journal of Preventive Cardiology 24, 22-28.

Covas, M., Nyussinen, K., Poulsen, H. E., Kaikkonen, J., Zanfi, H. F., Kiesewetter, H., Gaddi, A., de la Torre, R., Mursu, J., Bäumler, H., Nascetti, S., Salonen, J. T., Fitió, M., Virtanen, J., Marrugat, J. and for the EUROLIVE Study Group (2006) The effect of polyphenols in olive oil on heart disease risk factors. Annals of Internal Medicine 145, 333.

Criqui, M. H. and Aboyans, V. (2015) Epidemiology of peripheral artery disease. Circulation Research 116, 1509-1526.

Dardano, A., Penno, G., Del Prato, S. and Micocci, R. (2014) Optimal therapy of type 2 diabetes: A controversial challenge. Aging (Albany NY) 6, 187-206.

Das, U. N. (2008) Essential fatty acids and their metabolites could function as endogenous HMG-CoA reductase and ACE enzyme inhibitors, anti-arrhythmic, anti-hypertensive, anti-atherosclerotic, anti-inflammatory, cytoprotective, and cardioprotective molecules. Lipids in Health and Disease 7, 37.

Delaney, C. L., Smale, M. K. and Miller, M. D. (2019) Nutritional considerations for peripheral arterial disease: A narrative review. Nutrients 11, 1219.

Diabetes Prevention Program Research Group (2009) 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. The Lancet 374, 1677-1686.

Dionisio, N., Jardim, I., Salido, G. M. and Rosado, J. A. (2010) Homocysteine, intracellular signaling and thrombotic disorders. Current Medicinal Chemistry 17, 3109-3119.

Donnan, G. A., Davis, S. M., Chambers, B. R. and Gates, P. C. (1998) Surgery for prevention of stroke. The Lancet (London, England) 351, 1372-1373.

Donnan, P. T., Thomson, M., Fowkes, F. G., Prescott, R. J. and Housley, E. (1993) Diet as a risk factor for peripheral arterial disease in the general population: The Edinburgh artery study. The American Journal of Clinical Nutrition 57, 917-921.

Fahrleitner, A., Dobnig, H., Obermosterer, A., Pilger, E., Leb, G., Weber, K., Kudlacek, S. and Obermayer-Pietsch, B. (2002) Vitamin D deficiency and secondary hyperparathyroidism are common complications in patients with peripheral arterial disease. Journal of General Internal Medicine 17, 663-669.

Falcone Ferreyra, M. L., Rius, S. P. and Casati, P. (2012) Flavonoids: biosynthesis, biological functions, and biotechnological applications. Frontiers in Plant Science 3, 222.

Falah, B., Souza-Barbos, J., Cucato, G., Chehuem, M., Gobbo, L., Wolosker, N., Forjaz, C. and Ritti-Dias, R. (2013) Predictors of walking capacity in peripheral arterial disease patients. Circulation 128, 857-857.

Fields, R., Brook-Barclay, L., Delaney, C. L., Spark, J. I. and Miller, M. D. (2018) Nutritional considerations for peripheral arterial disease: A narrative review. The Journal of the American College of Cardiology 71, 2064.

Fowler, R., Chua, G. T., Salcuni, M., Siani, A., Giacco, A., Donati, M. B., De Gaetano, G., Capani, F., Iacoviello, L. and Gendiabe, I. (2003) A high-score mediterranean dietary pattern is associated with a reduced risk of peripheral arterial disease in Italian patients with type 2 diabetes. Journal of Thrombosis and Haemostasis 1, 1744-1752.

Flock, M. R., Skulas-Ray, A. C., Harris, W. S., Etherton, T. D., Flemig, D. and Miller, M. D. (2019) Nutritional considerations for peripheral arterial disease: A narrative review. Annals of Vascular Surgery 32, 145-175.

Flock, M. R., Skulas-Ray, A. C., Harris, W. S., Etherton, T. D., Flemig, D. and Miller, M. D. (2019) Nutritional considerations for peripheral arterial disease: A narrative review. Annals of Vascular Surgery 32, 145-175.

Flock, M. R., Skulas-Ray, A. C., Harris, W. S., Etherton, T. D., Flemig, D. and Miller, M. D. (2019) Nutritional considerations for peripheral arterial disease: A narrative review. Annals of Vascular Surgery 32, 145-175.

Flock, M. R., Skulas-Ray, A. C., Harris, W. S., Etherton, T. D., Flemig, D. and Miller, M. D. (2019) Nutritional considerations for peripheral arterial disease: A narrative review. Annals of Vascular Surgery 32, 145-175.

Flock, M. R., Skulas-Ray, A. C., Harris, W. S., Etherton, T. D., Flemig, D. and Miller, M. D. (2019) Nutritional considerations for peripheral arterial disease: A narrative review. Annals of Vascular Surgery 32, 145-175.
Kokkinidis, D. G., Strobel, A., Jawaid, O., Haider, M. N., Alvandi, B., Singh, G. D., Laird, J. R., Waldo, S. W. and Armstrong, E. J. (2020) Development and validation of a predictive score for anterograde crossing of infraepigastric chronic total occlusions: (The Infraop-CTO Score). Catheterization and Cardiovascular Interventions 95, 748-755.

Koutsoumpelis, A., Argyriou, C., Tasopoulou, K. M., Katsouyanni, K., Petridou, E. and Trichopoulos, D. (2006) Flavonoid classes and risk of peripheral arterial occlusive disease: a case–control study in Greece. European Journal of Clinical Nutrition 60, 214-219.

Lane, J. S., Magni, C. P., Lane, K. T., Chan, T., Hoyt, D. B. and Greenfield, S. (2008) Nutrition impacts the prevalence of peripheral arterial disease in the United States. Journal of Vascular Surgery 48, 897-904.

Lemopoulos, I. G., van Meijel, R. L. J., Manolopoulos, K. N. and Goossens, G. H. (2020) Oxygenation of adipose tissue: A human perspective. Acta Physiologica 228, e13298.

Leng, G. C., Horrobin, D. F., Fowkes, F. G., Smith, F. B., Lowe, G. D., Donnan, P. T. and Ellis, K. (1994) Plasma essential fatty acids, cigarette smoking, and dietary antioxidants in peripheral arterial disease. A population-based case-control study. Arteriosclerosis and Thrombosis 14, 471-478.

Leng, G. C., Lee, A. J., Fowkes, F. G. R., Jesop, R. G., Lowe, G. D. O., Skinner, E. R. and Mowat, B. F. (1998) Randomized controlled trial of gamma-linolenic acid and eicosapentaenoic acid in peripheral arterial disease. Clinical Nutrition 17, 265-271.

Leng, G. C., Lee, A. J., Fowkers, F. G. R., Whiteman, M., Dunbar, J., Housley, E. and RuckleV, C. V. (1996) Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general population. International Journal of Epidemiology 25, 1172-1181.

Levitan, E. B., Ahmed, A., Amett, D. K., Polak, J. F., Hundle, W. G., Blumenk, D. A., Heckbert, S. R., Jacobs, D. R. and Nettleton, J. A. (2016) Mediterranean diet score and left ventricular structure and function: the Multi-Ethnic Study of Atherosclerosis. The American Journal of Clinical Nutrition 104, 595-602.

Lin, S. V. Y., Lee, W. R., Su, Y. F., Hsu, S. P., Lin, H. C., Ho, P. Y., Hou, T. C., Chou, P., Kuo, C. T. and Lee, W. S. (2012) Folic acid inhibits endothelial cell proliferation through activating the cSrc/ERK 2/NF-kB/p53 pathway mediated by folic acid receptor. Angiogenesis 15, 671-683.

Look AHEAD Research Group, Wing, R. R., Bolin, P., Brancati, F. L., Bray, G. A., Clark, J. M., Coday, M., Crow, R. S., Curtis, J. M., Egan, C. M., Espeland, M. A., et al. (2013) Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. The New England Journal of Medicine 369, 145-154.

Luu, N. T., Madden, J., Calder, P. C., Grimbble, R. F., Shearman, C. P., Chan, T., Tull, S. P., Dastur, N., Rainger, G. E. and Nash, G. B. (2007) Comparison of the pro-inflammatory potential of monocytes from healthy adults and those with peripheral arterial disease using an in vitro culture model. Atherosclerosis 193, 259-268.

Madden, J., Brunner, A., Dastur, N. D., Tan, R. M., Nash, G. B., Ed Rainger, G., Shearman, C. P., Calder, P. C. and Grimbble, R. F. (2007) Fish oil induced increase in walking distance, but not ankle brachial pressure index, in peripheral arterial disease is dependent on both body mass index and inflammatory genotype. Prostaglandins, Leukotrienes and Essential Fatty Acids 76, 331-340.

Madden, J., Shearman, C. P., Dunn, R. L., Dastur, N. D., Tan, R. M., Nash, G. B., Rainger, G. E., Brunner, A., Calder, P. C. and Grimbble, R. F. (2009) Altered Monocyte Cd44 expression in peripheral arterial disease is corrected by fish oil supplementation. Nutrition, Metabolism, and Cardiovascular Diseases 19, 247-252.

Malinowski, B., Zalewska, K., Węsierska, A., Sokolowska, M. M., Socha, M., Liczner, G., Pawlak-Osinska, K. and Wiciński, M. (2019) Intermittent fasting in cardiovascular disorders—an overview. Nutrients 11, 673.

Martinez-Gonzalez, M. A., Ros, E. and Estruch, R. (2018) Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. The New England Journal of Medicine 379, 1388-1389.

Martinez-Gonzalez, M. A., Salas-Salvadó, J., Estruch, R., Corella, D., Fito, M. and Ros, E. (2015) Benefits of the Mediterranean diet: Insights from the predimed study. Progress in Cardiovascular Diseases 58, 50-60.

Massaro, M., Scoditti, E., Carluccio, M. A. and De Caterina, R. (2010) Nutraceuticals and prevention of atherosclerosis: focus on omega-3 polyunsaturated fatty acids and Mediterranean diet polyphenols. Cardiovascular Therapeutics 28, e13-e19.

Mattson, M. P., Allison, D. B., Fontana, L., Harvie, M., Longo, V. D., Malaisse, W. J., Mosley, M., Notterpek, L., Ravussin, E., Scheer, F. A. J. L., Seyfried, T. N., Varady, K. A. and Panda, S. (2014) Meal frequency and timing in health and disease. Proceedings of the National Academy of Sciences 111, 16647-16653.

Maugeri, A., Barchitta, M., Kunzova, S., Bauerova, H., Agodi, A. and Vinciguerra, M. (2020) The association of social and behavioral factors with dietary risks in adults: Evidence from the kardiovize brno 2030 study. Nutrition, Metabolism, and Cardiovascular Diseases 30, 896-906.

Maugeri, A., Hruskova, J., Jakubik, J., Hlinomaz, O., Medina-Inojosa, J. R., Barchitta, M., Agodi, A. and Vinciguerra, M. (2019) How dietary patterns affect left ventricular structure, function and remodelling: evidence from the Kardiovize Brno 2030 study. Scientific Reports 9, 19154.

Meier, T., Gräfe, K. S., Senn, F., Sur, P., Stangl, G. I., Dawczynski, C., Mars, W., Kleber, M. E. and Lorkowski, S. (2019) Cardiovascular mortality attributable to dietary risk factors in 51 countries in the WHO European Region from 1990 to 2016: a systematic analysis of the Global Burden of Disease Study. European Journal of Epidemiology 34, 37-55.

Malamé, M. L., Muntner, P., Michos, E. D., Urbarri, J., Weber, C., Sharma, J. and Raggi, P. (2008) Serum 25-hydroxyvitamin D levels and the prevalence of peripheral arterial disease. Arteriosclerosis, Thrombosis, and Vascular Biology 28, 1179-1185.

Menzel, T., Lührs, H., Zirlik, S., Schaub, J., Kudlich, T., Gerke, T., Göstner, A., Neumann, M., Melcher, R. and Scheppach, W. (2004) Butyrate inhibits leukocyte adhesion to endothelial cells via modulation of VCAM-1. Inflammatory Bowel Diseases 10, 122-128.

Merchant, A. T., Hu, F. B., Spiegelman, D., Willett, W. C., Rimm, E. B. and Ascherio, A. (2004) Dietary fiber reduces peripheral arterial disease risk in men. The Journal of Nutrition 133, 3658-3663.

Merchant, A. T., Hu, F. B., Spiegelman, D., Willett, W. C., Rimm, E. B. and Ascherio, A. D. (2003) The use of B vitamin supplements and peripheral arterial disease risk in men are inversely related. The Journal of Nutrition 133, 2863-2867.

Miller, M., Delaney, C., Penna, D., Liang, L., Thomas, J., Puckridge, P. and Spark, J. I. (2012) A 3-year follow-up study of inpatients with lower limb ulcers: Evidence of an obesity paradox? Journal of Multidisciplinary Healthcare 5, 181-186.

Miraščiški, U., Martin, A., Jorgensen, L. N., Sampson, B. and Ågren, M. S. (2013) Zinc, copper, and selenium tissue levels and their relation to subcutaneous abscess, minor surgery, and wound healing in humans. Biological Trace Element Research 153, 76-83.

Naqvi, A. Z., Davis, R. B. and Mukamal, K. J. (2014) Nutrient intake and peripheral arterial disease in adults: Key considerations in cross-sectional studies. Clinical Nutrition 33, 443-447.

Naude, C. E., Schoonees, A., Senekal, M., Young, T., Garner, P. and Volmink, J. (2014) Low Carbohydrate versus isoenergetic balanced diet: A systematic review and meta-analysis. PLoS One 9, e100652.
Neeleman, T. N. J., Ross, R. R., Després, J., Matsuzawa, Y., Yamashita, S., Shai, I., Seidell, J., Magni, P., Santos, R. D., Arsenault, B., Cuebas, A., Hu, F. B., Griffin, B., Zambon, A., Barter, P., Fruchart, J. and Eckel, R. H. (2019) Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: A position statement. The Lancet Diabetes & Endocrinology 7, 715-725.

Norgren, L., Hiatt, W. R., Dormandy, J. A., Nehler, M. R., Harris, K. A., Fowkes, F. G. R. and Rutherford, R. B. (2007) Inter-society consensus for the management of peripheral arterial disease. International Angiology 26, 81-157.

Nosova, E. V., Conte, M. S. and Grenon, S. M. (2015) Advancing beyond the “heart-healthy diet” for peripheral arterial disease. Journal of Vascular Surgery 61, 265-274.

Ogumoroti, O., Michos, E. D., Aronis, K. N., Salami, J. A., Blankstein, R., Virani, S. S., Spatz, E. S., Allen, B. N., Rana, J. S., Blumenthal, R. S., Veledar, E., Szklo, M., Blaha, M. J. and Nasir, K. (2018) Life’s simple 7 and the risk of atrial fibrillation: The multi-ethnic study of atherosclerosis. Atherosclerosis 275, 174-181.

Palaioyannis, L., Kokkinidis, D. G., Li, W., Karamanis, D., Ognibene, J., Arora, S., Southern, W. N. and Mantzoros, C. S. (2020) Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. Metabolism 108, 154262.

Patterson, E., Wall, R., Fitzgerald, G. F., Ross, R. P. and Stanton, C. (2012) Health implications of high dietary omega-6 polysaturated fatty acids. Journal of Nutrition and Metabolism 2012, 539426.

Planavila, A., Redondo, I., Hondares, E., Vinciguerra, M., Muntis, C., Iglesias, R., Gabrieli, L. A., Stiges, M., Giralt, M., van Bilzen, M. and Villarroya, F. (2013) Fibroblast growth factor 21 protects against cardiac hypertrophy in mice. Nature Communications 4, 2019.

Polonsky, T. S., Tian, L., Zhang, D., Bazzano, L. A., Criqui, M. H., Ferrucci, L., Guralnik, J. M., Kibbe, M. R., Leeuwenburgh, C., Sufti, R. L. and McDermott, M. M. (2019) Associations of weight change with changes in calf muscle characteristics and functional decline in peripheral artery disease. Journal of the American Heart Association 8, e010890.

Rathod, K. S., Velmurugan, S. and Ahluwalia, A. (2016) A ‘green’ diet-based approach to cardiovascular health? Is inorganic nitrates the answer? Molecular Nutrition & Food Research 60, 185-202.

Rimb, E. B., Appel, L. J., Chiue, S. E., Djoussé, L., Engler, M. B., Krist-Etherton, P. M., Mozaffarian, D., Siscovick, D. S., Lichtenstein, A. H. and On behalf of the American Heart Association Nutrition Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Epidemiology and Prevention; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology (2018) Nutrition and atherosclerosis. Journal of the American Medical Association 311, 415-417.

Ruiz-Canela, M., Estruch, R., Corella, D., Salas-Salvadó, J. and Martinez-González, M. A. (2014) Association of Mediterranean Diet With Peripheral Artery Disease. Journal of the American Medical Association 311, 553-559.

Ruiz-Canela, M. and Martinez-González, M. A. (2014) Lifestyle and dietary risk factors for peripheral artery disease. Circulation Journal 78, 553-559.

Russell, L. (2001) The importance of patients’ nutritional status in wound healing. British Journal of Nursing 10, S42-S49.

Russo, G. L. (2009) Dietary n-6 and n-3 polysaturated fatty acids: From biochemistry to clinical implications in cardiovascular prevention. Biochemical Pharmacology 77, 937-946.

Sabeva, N. S., McPhaul, C. M., Li, X., Cory, T. J., Feola, D. J. and Graf, G. A. (2011) Phytosterols differentially influence ABC transporter expression, cholesterol efflux and inflammatory cytokine secretion in macrophage foam cells. The Journal of Nutritional Biochemistry 22, 777-783.

Salomon du Mont, L., Leclerc, B., Morgant, M., Besch, G., Laubriet, A., Steinmetz, E. and Rinckenbach, S. (2017) Impact of nutritional state on critical limb ischemia early outcomes (demarcite trial). Annals of Vascular Surgery 45, 10-15.

Schano, V., Masero-Acebal, E., Logroscino, G., De Maio, J. J., Lanero, S., Scoppa, F. and Chiariello, M. (2008) Omega-3 polysaturated fatty acid in peripheral arterial disease: Effect on lipid pattern, disease severity, inflammation profile, and endothelial function. Clinical Nutrition 27, 241-247.

Selvin, E. and Erlinger, T. P. (2004) Prevalence of and risk factors for peripheral arterial disease in the United States: Results from the national health and nutrition examination survey, 1999-2000. Circulation 110, 738-743.

Shulman, G. I. (14) Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. New England Journal of Medicine 371, 1131-1141.

Siassos, G., Skotsimas, G., Oikonomou, E., Sagris, M., Vasiliki-Chara, M., Bletsas, E., Stampoulouglou, P., Theofilis, P., Charalampous, G. and Tousoulis, D. (2020) Anti thrombotic treatment in diabetes mellitus: a review of the literature about antplatelet and anticoagulation strategies used for diabetic patients in primary and secondary prevention. Current Pharmaceutical Design 26, 2780-2788.

Singer, D. R. J. and Kite, A. (2008) Management of hypertension in peripheral arterial disease: does the choice of drugs matter? European Journal of Vascular and Endovascular Surgery 35, 701-708.

Singhal, A., Lanigan, J., Storry, C., Low, S., Birbara, T., Lucas, A. and Deanfield, J. (2013) Docosahexaenoic acid supplementation, vascular function and risk factors for cardiovascular disease: A randomized controlled trial in young adults. Journal of the American Heart Association 2, e00283.

Sparks, L. M., Xie, H., Koza, R. A., Mynatt, R., Hulver, M. W., Bray, G. A. and Smith, S. R. (2005) A High-fat diet coordinately downregulates genes required for mitochondrial oxidative phosphorylation in skeletal muscle. Diabetes 54, 1926-1933.

Sugai, T., Watanabe, T., Otaki, Y., Goto, J., Watanabe, K., Toshima, T., Takahashi, T., Yokoyama, M., Tamura, H., Nishiyama, S., Ariimoto, T., Takahashi, H., Shishido, T. and Watanabe, M. (2018) Decreased posa muscle computed tomography value predicts poor outcome in peripheral artery disease. Circulation Journal 82, 3069-3075.

Sugita, T., Yoshikawa, D., Ishii, H., Suzuki, S., Kumagai, S., Inoue, Y., Okumura, S., Isobe, S., Hayashi, M., Ando, H., Amano, T. and Murohara, T. (2015) Relation of omega-3 fatty acid and C-reactive protein to peripheral artery disease in patients with coronary artery disease. Heart and Vessels 29, 449-455.

Thomas, J., Delaney, C., Suen, J. and Miller, M. (2019) Nutritional status of patients admitted to a metropolitan tertiary care vascular surgery unit. Asia Pacific Journal of Clinical Nutrition 28, 64-71.

Tinsley, G. M. and Horne, B. D. (2018) Intermittent fasting and cardiovascular disease: current evidence and unresolved questions. Future Cardiology 14, 47-54.

Trowall, M. E., Virtamo, J., Haukka, J. K., Aro, A., Albanes, D. and Huttenen, J. K. (2000) Prospective study of diet, lifestyle, and intermittent claudication in male smokers. American Journal of Epidemiology 151, 892-901.

Torres, N., Guevara-Cruz, M., Velázquez-Villegas, L. A. and Tovar, A. R. (2015) Nutrition and atherosclerosis. Archives of Medical Research 46, 408-426.

Tuso, P., Stoll, S. R. and Li, W. W. (2015) A plant-based diet, atherogenesis, and coronary artery disease prevention. The Permanente Journal 19, 62-67.

Tsoukalas, I., Murray, G. D., Lee, A. J., Rumley, A., Lowe, G. D. O. and Fowkes, F. G. R. (2005) C-reactive protein, interleukin-6, and soluble adhesion molecules as predictors of progressive peripheral atherosclerosis in the general population. Circulation 112, 976-983.

Unkurt, J. T., Allison, M. A., Criqui, M. H., McDermott, M. M., Wood, A. C., Folsom, A. R., Lloyd-Jones, D., Rasmussen-Torvik, L. J., Allen, N., Burke, G., Szklo, M., Cushman, M., McClelland, R. L. and Wassel, C. L. (2019) Life’s simple 7 and peripheral artery disease: The multi-ethnic study of atherosclerosis. American Journal of Preventive Medicine 56, 262-270.
Veech, R. L. (2004) The therapeutic implications of ketone bodies: the effects of ketone bodies in pathological conditions: ketosis, ketogenic diet, redox states, insulin resistance, and mitochondrial metabolism. *Prostaglandins, Leukotrienes and Essential Fatty Acids* 70, 309-319.

Villacorta, L., Graça-Souza, A. V., Ricciarelli, R., Zingg, J. and Azzi, A. (2003) Alpha-tocopherol induces expression of connective tissue growth factor and antagonizes tumor necrosis factor-alpha-mediated downregulation in human smooth muscle cells. *Circulation Research* 92, 104-110.

Wall, R., Ross, R. P., Fitzgerald, G. F. and Stanton, C. (2010) Fatty acids from fish: the anti-inflammatory potential of long-chain omega-3 fatty acids. *Nutrition Reviews* 68, 280-289.

Wang, T. J., Pencina, M. J., Booth, S. L., Jacques, P. F., Ingelsson, E., Lanier, K., Benjamin, E. J., D’Agostino, R. B., Wolf, M. and Vasan, R. S. (2008) Vitamin D deficiency and risk of cardiovascular disease. *Circulation* 117, 503-511.

Wilmink, A. B. M., Welch, A. A., Quick, C. R. G., Burns, P. J., Hubbard, C. S., Bradbury, A. W. and Day, N. E. (2004) Dietary folate and vitamin b6 are independent predictors of peripheral arterial occlusive disease. *Journal of Vascular Surgery* 39, 513-516.

Wischmeyer, P. E., Carli, F., Evans, D. C., Guilbert, S., Kozar, R., Pryor, A., Thiele, R. H., Everett, S., Grocott, M., Gan, T. J., Shaw, A. D., Thacker, J. K. M., Miller, T. E., Hedrick, T. L., McEvoy, M. D., Mythen, M. G., Bergamaschi, R., Gupta, R., Holubar, S. D., Senagore, A. J., Abola, R. E., Bennett-Guerrero, E., Kent, M. L., Feldman, L. S. and Fiore, J. F. (2018) American society for enhanced recovery and perioperative quality initiative joint consensus statement on nutrition screening and therapy within a surgical enhanced recovery pathway. *Anesthesia & Analgesia* 126, 1883-1895.

Yamakuchi, M., Bao, C., Ferlito, M. and Lowenstein, C. J. (2008) Epigalocatechin gallate inhibits endothelial exocytosis. *Biological Chemistry* 389, 93.