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The impact of a vegetarian diet in cardiovascular risk

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Abstract

Introduction: Cardiovascular disease is a leading cause of death and chronic disability, and optimizing its prevention and management remains a priority. A positive influence of following a vegetarian diet concerning cardiovascular health was already explained by several mechanisms. However, a restrictive diet may raise some concerns regarding specific macro and micronutrient deficiencies. This review aims to provide a critical analysis on the positive and negative aspects concerning the impact of a vegetarian diet in cardiovascular risk.

Methods: A literature search was performed in PubMed database with the keywords «vegetarian diet» and «cardiovascular disease». Among the initial 557 articles, 54 were left as starting database, along with European Society of Cardiology Guidelines on cardiovascular disease prevention. Posteriorly, 13 extra articles were added from their bibliographical references, reaching a 68 articles database for this review.

Results: Overall, vegetarian population presents with better cardiovascular risk profile, expressed by lower BMI, better blood pressure control, reduced pro-atherogenic lipids and better glycaemic control and insulin sensitivity. Other recently investigated atherogenic paths seem to be positively influenced, such as chylomicron remnants removal from circulation, oxidative and inflammation profile, blood fluidity and intestinal microbiota. Furthermore, imaging methods have shown better structural and functional vascular properties among vegetarians. On the other hand, a non-balanced vegetarian diet might lead to nutrients deficit, which could nullify these advantages. Among these concerns are vitamin B12, essential amino acids and protein, n-3 fatty acids, iron and vitamin D shortage. These limitations may be overcome through a carefully planned diet and, in some cases, the use of supplements or fortified foods. Ultimately, this potential beneficial effect is associated with a healthy vegetarian concept, with scarce intake of refined and processed food products, avoiding overconsumption of sugar and trans fats.

Conclusion: A vegetarian diet brings a positive impact in several independent cardiovascular risk factors. Despite the additional challenge in reaching specific macro and micronutrients which are less available in plant-based foods, their shortage can be avoided by planning a well-balanced and complete diet, based on healthy and natural food components. As there is the acknowledgment of its limitations and corresponding precautions are taken, a vegetarian diet could be used as an effective weapon towards prevention and management of cardiovascular disease.

Keywords: Cardiovascular Diseases; Risk Factors; Diet, Vegetarian; Vegetarians; Nutrition Therapy.

Introduction

Cardiovascular disease presents itself as a leading global cause of death and chronic disability. In 2015, this group of pathologies is estimated to have killed over 17 million people all over the world.[1] Every minute someone dies from a heart disease related event.[2] These alarming numbers make clear the need to optimize health care, not only with an early and effective treatment but specially by enhancing prevention.

Nutritional patterns have been connected to cardiovascular disease for many years. It has already been demonstrated that dietary factors among other pieces of a healthy lifestyle can largely contribute to reduce both incidence and mortality associated to the cardiovascular system.[3]

However, dietary plans are not addressed enough by healthcare providers during medical contact with their patients, probably due to their unawareness of the actual best pattern to follow. Its value goes beyond macro and micronutrients individually ingested, since this perspective does not account for their potentially synergistic interaction. This means the whole nutritional pattern is important, and it might work as a prevention and treatment target.[4]

The Mediterranean diet has been one of the most investigated approaches in preventing heart disease. Evidence has been found supporting its relationship with reduced weight, body mass index (BMI) and waist circumference, lower total cholesterol levels and increased high density lipoprotein cholesterol (HDL-C) ones, and even a lower risk of diabetes with better glycaemic control and diminished insulin resistance.[5]

Following a vegetarian diet means that one does not eat flesh from any animal, including meat or meat products, poultry, fish and seafood.[6] There is not only a singular vegetarian diet – for example, ovo-lacto-vegetarian diets allow the ingestion of eggs, milk and dairy products, while having a vegan diet means one does not eat these food items.[7] However, they all share with the Mediterranean diet many ground components, such as fruits, vegetables, whole grains, legumes and nuts. These were proven to contribute to the reduction of cardiovascular disease morbidity and mortality through a great variety of risk factors, in all kinds of plant-based patterns.[4,8]

Several studies have found a positive impact of vegetarian diets in metabolic profiles and classic modifiable cardiovascular risk factors, such as lipid profile, body mass index, blood pressure and diabetes.[9,10] Also, recent researches begin to propose new influencing mechanisms and representative biomarkers.[11-13]

On the other hand, it also raises some concerns about specific macro and micronutrient deficiencies, namely protein, some essential fatty acids, iron, vitamin B12, among other metabolic modifications.[9]

The goal of this review is to perform a critical analysis on the impact a vegetarian diet might have in cardiovascular risk. We aim to evaluate whether the advantages of a vegetarian diet concerning cardiovascular health surpass its possible risks, and in what way it might be used as a preventive weapon against cardiovascular events.

Materials and methods

A literature search was developed through PubMed database using the keywords «vegetarian diet» and «cardiovascular disease», obtaining a total of 557 results. Among these, only articles written in English during the last 5 years were selected.

The 125 articles obtained were posteriorly reviewed in order to select only the ones focusing on the association between a vegetarian diet or its main components and cardiovascular diseases or their modifiable risk factors. This analysis led to the exclusion of 71 articles, concerning other influencing factors of cardiovascular risk such as other dietary patterns or genetic polymorphisms (21), regarding other non-communicable diseases such as chronic kidney disease, Alzheimer's disease, hyperthyroidism, among others (38), or that simply were not suitable for the purposes of this review (12).

The remaining 54 were then used as starting database for the investigation, together with European Society of Cardiology (ESC) Guidelines on cardiovascular disease prevention for a deeper knowledge about the approached risk factors.[14] During the writing process, 13 more articles were added from the reference list of the above-mentioned articles for better understanding of some considerations. In the end, 68 articles contributed to this narrative review's construction and improvement (Fig.1).

Our study intends to present some pros and cons in adopting a vegetarian diet concerning cardiovascular health. We will separately present by topics the impact of this nutritional pattern in classical cardiovascular risk factors, some ground-breaking influencing approaches, and we will also alert to some possible shortfalls that must be taken into account.

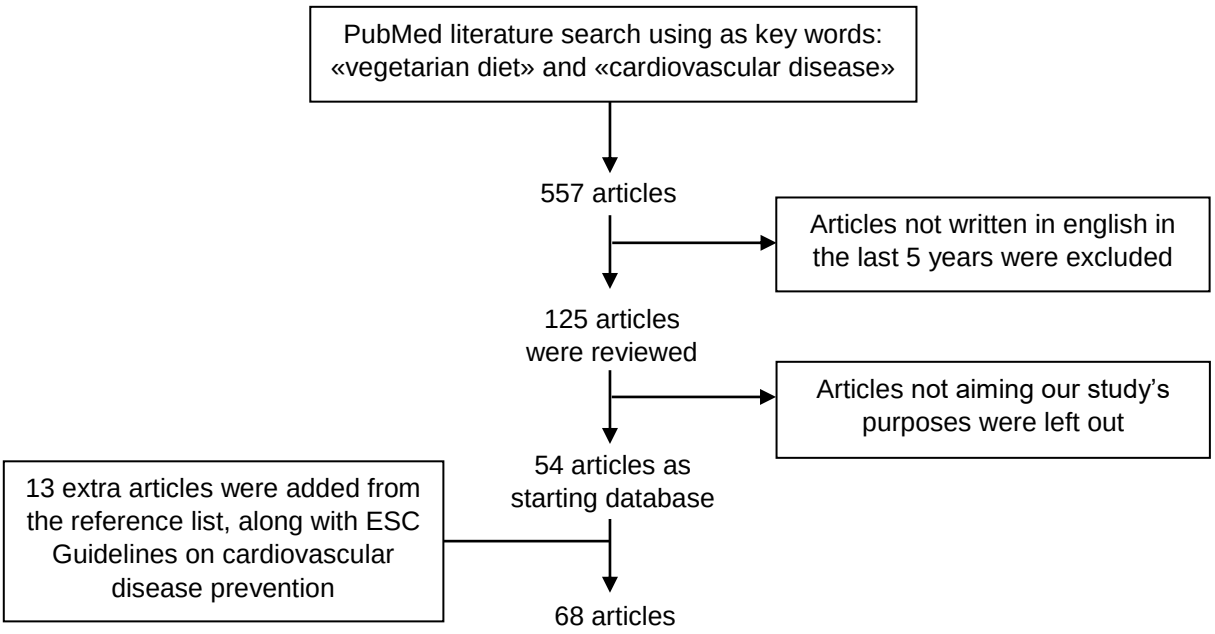

Figure 1 – Selection method of approached articles.

Results

Atherosclerosis is a major piece responsible for cardiovascular disease development, and it is known to be influenced by several risk factors, being cholesterol considered for a long time as the principal responsible, but always alongside blood pressure, diabetes, obesity, family history, smoking and nutritional pattern. These are all contributory causes of a complex mechanism, which is why we cannot point one single explanation out. It includes vascular endothelial cell injury and dysfunction, low density lipoprotein cholesterol (LDL-C) oxidation and macrophage activation, that lead to foam cells formation then covered with a fibrous cap that may become unstable and rupture. Increased blood pressure, for example, not only accelerates atherosclerosis in the large arteries but also causes arteriolar hyaline changes.[13,15]

Throughout time, many methods of assessing cardiovascular risk have been developed. SCORE system is the recommended one in Europe, since it is based on representative European cohort datasets. It calculates the 10-year risk of a first deadly atherosclerotic event, including coronary artery disease, stroke and aneurysm of the abdominal aorta. The main variables that are used by SCORE are: sex, age, total cholesterol or total cholesterol/HDL-C ratio, systolic blood pressure and smoking status. However, this is merely an estimation system, and cardiovascular risk is the result of multiple interacting risk factors.[14]

Vegetarian population has been shown to present a better cardiovascular risk biomarker profile, expressed by a lower BMI, systolic and diastolic blood pressure, pro-atherogenic lipids, apolipoprotein B and blood glucose.

Furthermore, in order to improve cardiovascular risk stratification, imaging methods have been used to assess early stages of cardiovascular disease while it is still silent. They allow the evaluation of arterial stiffening and structural and functional properties of carotid arteries, using their thickness and distensibility, which are related to future cardiovascular events. In the absence of classical risk factors like hypertension, dyslipidemia and diabetes, subclinical vascular disease also seems to be reduced in vegetarian men. This discrepancy remained after the adjustment for physical activity level, age, systolic blood pressure and BMI, and it was detected an independent association between this dietary pattern and reduced aortic stiffness.[16]

Cholesterol

Total Cholesterol and LDL-C

There is a strong and graded positive association between total cholesterol and cardiovascular disease risk. It is well known that along with the plasmatic total amount of cholesterol, the differential between its subtypes is also of extreme importance – the lipid pattern. Most cholesterol is normally carried in LDL-C molecules. Higher levels of plasmatic LDL-C are known roots to atherosclerosis, and evidence that its reduction decreases cardiovascular risk is unequivocal.[14]

Vegetarian diets can reduce total cholesterol and LDL-C plasmatic concentrations. This might occur because they are usually low in fat, specially saturated fatty acids.[17]

Concerning cardiovascular protection, saturated fatty acid ingestion should not exceed 10% of a daily diet, and polyunsaturated ones should be preferred instead.[14] It has been shown that replacing saturated fats with vegetable oils rich in polyunsaturated fatty acids brings significant impact in heart disease prevention, specially by lowering LDL-C levels, with a reduction of cardiovascular risk of about 10%, comparable to a statin effect.[18]

The principal sources of saturated fat are dairy and meat.[19] Therefore, a lack of ingestion of these products might be advantageous to cardiovascular disease avoidance. When major sources of protein change from red meat to nuts and fish, saturated fat, heme-iron and sodium all decrease, while polyunsaturated fats increase.[20]

Comparison with carbohydrates' intake has also been done, leading to the conclusion that substituting 1% of carbohydrates in daily intake by polyunsaturated fats results in a 0,9 mg/dL decrease in LDL cholesterol.[19]

Besides, a plant-based diet is high in fibre and many phytochemicals that are able to reduce intestinal absorption of cholesterol molecules.[17] Among these phytochemicals there are phytosterols, which have been shown to decrease LDL-C levels by an average of 10% when ingested around 2 g/day, in addition to the reduction that can already obtained through a low-fat diet. Phytosterols' intake among vegetarians is almost two times greater than in a omnivores, which is round about 200-400 mg/day.[21]

These effects can be obtained through consumption of soy and non-soy legumes, which are a frequent source of protein intake among vegetarians.[22]

HDL

HDL-C plasmatic levels, on the other hand, might be inversely correlated with cardiovascular events, which could be explained by its functions – cholesterol esterification and reverse transportation of cholesterol, made from tissues to the liver, which leads to its elimination. Low

HDL-C is thought to be associated with increased cardiovascular risk, even though manoeuvres to increase it have not shown a decreasing in this risk.[7,23]

Concerning HDL-C the results are not consensual. Some studies came to the conclusion that vegetarian diets are prone to lower plasmatic HDL-C, but in some other ones there was no evidence that its concentrations differed in vegetarians and omnivores.[17]

On a specific study, a randomised controlled trial based on a 12-week vegetarian diet but with the particularity of being low in fat (representing only 7-15% of calorie intake), HDL-C tended to decrease which could be a disadvantage to cardiovascular health.[24]

Saturated fats increase HDL-C, as well as polyunsaturated fat even though in a smaller scale, which might be the explanation for this diversity. On this specific topic it is important to consider the subtype of vegetarian diet. Ovo-lacto-vegetarians have higher saturated fat and cholesterol intake than vegans, because they include egg yolk, milk and dairy products in their nutritional routine.[7] Contrastingly, a vegan person does not consume these products that contribute greatly to HDL-C, and on that account they can reach lower values. Additionally, a great part of HDL-C levels variations in humans are genetically determined.[23]

As will be further explained below, vegetarians tend to get lower intakes of vitamin B12. Low levels of HDL may have as another underlying cause vitamin B12 deficiency, explained by a downregulation of peroxisome proliferator-activated receptor a (PPAR a), which is responsible for HDL's major protein component synthesis, apolipoprotein A1.[25]

Despite this tendency to a lower amounts of HDL-C, studies show vegetarians still achieve a lower TC: HDL ratio.[26]

Also, it has been shown that having low HDL due to reduced fat intake is not associated with diminished cardiovascular health.[10]

Triglycerides

Despite not being accounted for in SCORE system, plasmatic triglyceride levels are already well established as a significant biomarker of cardiovascular risk. Even though it is still under research, it is thought lipoproteins rich in triglycerides also contribute to atherosclerotic mechanism, as well as LDL-cholesterol. Saturated fat intake reduction contributes to a lower triglyceride level, but a higher intake of carbohydrates is associated to its increment, which is something to be aware of in a vegetarian diet.[19]

Studies about vegetarian diet and triglyceride plasmatic levels ended up creating a controversy. In some of them, a greater number of plasmatic triglycerides was achieved, but this is thought to be due to a higher ingestion of refined carbohydrates, fructose or saturated fats. This was particularly noticed in ovo-lacto-vegetarian diets.[10]

Despite the conflicting triglyceride levels when comparing vegetarians and omnivores' lipid profile, there were discovered potential advantages in taking either a vegan or an ovo-lacto-vegetarian diet concerning triglyceride-rich lipoproteins. During absorption of dietary fats two triglyceride-rich lipoproteins are produced: very low density lipoprotein (VLDL) and chylomicrons. The intravascular catabolism of those lipoproteins leads to the formation of remnants that can be potentially atherogenic by several mechanisms, if accumulated.

Remnants are taken up by macrophages and induce macrophage cholesterol accumulation and foam cell formation. They can also cause endothelium injury by inducting apoptosis, impair endothelium-dependent vasodilation, stimulate arterial smooth muscle cell proliferation, and even increase platelet aggregation.

Chylomicron remnants removal from the circulation seems to be done more efficiently among vegetarians, either vegans and ovo-lacto-vegetarians, which means they might have a positive impact in cholesterol homeostasis and atherosclerosis prevention.[7,27]

Apolipoprotein B and Apolipoprotein A1

Apolipoprotein B is the main apoprotein of atherogenic lipoproteins, and it appears to be a similar risk marker to LDL-C concerning cardiovascular disease. Apolipoprotein A1, on the contrary, is the major apoprotein of high-density lipoprotein, and its ratio with apolipoprotein B represents a very strong cardiovascular marker.[14]

A study comparing cardiovascular biomarkers between healthy vegetarians and omnivores, discovered lower levels of apolipoprotein B among vegetarians, contributing to a better cardiovascular risk biomarker profile.[16] Another cross-sectional study reported a significantly lower serum concentration of apolipoprotein B specifically in vegans when compared with omnivores, fish-eaters and other vegetarian patterns' users.[28]

Concerning apolipoprotein B: apolipoprotein A1 ratio, a significant difference has been detected between vegans and meat-eaters, even though comparison between apolipoprotein A1 amounts alone is not conclusive. In men there were no significant differences, but vegan women, after BMI adjustment, presented lower apolipoprotein A-1 than omnivore ones.[28]

Body Mass Index

BMI and central obesity are considered risk modifiers, associated with an increased risk of cardiovascular death. Energy intake should be done accordingly to the maintenance of a healthy BMI, which lies between 20 to 25 kg/m^2.

In addition to the amount of body fat, its distribution is important, and body fat stored in the abdomen carries a higher risk than subcutaneous fat. Therefore, waist-to-hip ratio and waist circumference are also important measurements with established thresholds.[14]

Excess adiposity increases cardiovascular risk by promoting dyslipidemia, hypertension, impaired glycaemic control, inflammation, obstructive sleep apnoea and associated hypoventilation and a prothrombotic state.[29]

Correlation has been made between obesity and a higher rate of cholesterol synthesis, added to an impaired clearance. Leptin is an adipocyte hormone which promotes hepatic cholesterol clearance. However, most obese subjects have leptin resistance and this effect is flawed, leading to a weaker lowering effect of a vegetarian diet on total cholesterol and non-HDL-C in a subpopulation of obese vegetarians.[17]

BMI and waist circumference have both been shown to be significantly lower in vegetarians when compared to non-vegetarians, even after age, sex, physical activities, alcohol consumption and education adjustment.[10,30]

On another level, as an intervention strategy, a meta-analysis of randomized controlled trials compared body weight changes in overweight populations with different vegetarian and non-vegetarian interventional diets, confirming a reduction of about 2 kg more in the first population. Among vegetarian individuals, interventions with vegan diets resulted in a greater weight loss than those with ovo-lacto-vegetarian diets.[31]

A six-month low-fat (7-15% of total energy) vegetarian diet, but without any calorie restriction or mandatory regular exercise, has been shown to lead to a significant BMI and weight reduction in an either overweight or obese population.

The mechanism behind this is probably the lower caloric density of the food consumed, but also the higher proportion of water and fibre, and it tends to be accentuated among vegans.[24]

Blood pressure

Vegetarian diets as well as other healthy dietary patterns are among the already well-established nutritional choices one can make to lower blood pressure, along with lower sodium intake, increased potassium ingestion and weight loss.[32]

It has been consistent over the years in several studies that vegetarians, and particularly vegans, have lower blood pressure levels and smaller preponderance of hypertension when compared to non-vegetarians. Vascular structural and functional changes have also been detected, namely a thinner intima-media thickness, reflecting a better endothelial and smooth muscle cells' function and arterial elasticity and vasodilation. Vasodilatory response and its degree has even been correlated to the vegetarian diet's time extent.[30]

This outcome might be partially related to a lower BMI detected in vegetarians, but differences in blood pressure between vegetarians and omnivores remain after age, sex and BMI are adjusted.[33]

Also, the higher intake of potassium through the ingestion of whole grains, fruits and vegetables in bigger proportions is likely to be a great contributing factor.[10]

New studies have recently discovered that dietary nitrate is able to reduce systolic blood pressure, especially along with antioxidants that support its reduction to nitric oxide (NO). It may additionally play a role against atherosclerosis by preventing adhesion of blood cells to the endothelium, and platelet aggregation.[2] The provision of dietary nitrate is mainly done by vegetables, and it has been shown that the average nitrate intake might triplicate in vegetarians, which might be one of the causes behind this community's blood pressure cut down.[33]

Even though with a lower strength of evidence, some studies have suggested that a higher intake of protein from plant sources, specially nuts, seeds and soy protein, can reduce blood pressure levels.[32] On the contrary, animal protein presents a direct relation with blood pressure's rise, mainly accounted by glycine, one of the predominant amino acids.[34]

Vegetarian diets have consistently been associated with decreased prevalence of insulin resistance, which is also believed to be a fundamental mechanism. This metabolic state might enhance sodium reabsorption in the kidney, leading to increased blood pressure.[30]

A recent study has gone even further, showing that a plant-based dietary intervention for four weeks might have a stronger impact lowering systolic and diastolic blood pressure than antihypertensive medication. A progressive reduction in that chronic stable medication use was made alongside blood pressure decreasing, and participant's blood pressure levels were better even after discontinuing it. This could mean that a well-defined plant-based diet could even be used as an effective antihypertensive therapeutic approach.[35]

Plasmatic glucose and Type 2 Diabetes Mellitus

Even though these findings are still inconclusive, it has recently been published that impaired glucose tolerance, even in non-diabetic population, might be modestly associated with an increased risk of cardiovascular disease mortality. At this point, lifestyle modifications such as better dietary options are essential to avoid type 2 diabetes mellitus.[36,37]

People with diabetes are at double the risk of cardiovascular morbimortality.[14,37] It has been shown that vegetarianism can lead to about 50% reduction in risk of diabetes, even in previously non-vegetarians who switch their diet to a vegetarian one. In fact, changing to a totally plant-based diet improves glycaemic control in weeks. Vegetarians tend to have lower BMI, and weight loss is generally accompanied by better glycaemic control and insulin sensitivity. However, according to the majority of reviewed studies on the topic, BMI seems to account for only a small percentage of the protective effect of a plant-based diet on diabetes.[38,39]

The mechanism behind this protective role, that appears to go beyond just BMI reduction, might be related to the type of foods predominantly ingested. The higher intake of whole grains and vegetables carries greater amounts of fibre, plant polyphenols and magnesium, that have been proven to affect insulin signalling and sensitivity and slow the rate of carbohydrate absorption. Furthermore, soy, a major source of protein in this population, has been shown to diminish insulin resistance when replacing meat.[39,40]

Additionally, regular consumption of meat is associated with an increased risk of diabetes. It is rich in saturated fats, which have been shown to trigger human B-cell apoptosis, responsible for insulin secretion.[39] Furthermore, it has also been stated that the dietary source of the fatty acids is of greater relevance, and the ones specifically held in meat are negatively associated with insulin secretion and sensitivity.[41]

Vegetarian diets seem to be helpful not only for prevention but also for treatment and prognosis of the already established disease. It was reported a significant reduction in plasma glucose levels and HbA_{1c} in patients with type 2 diabetes. A better glycaemic control in this population is essential to reduce the incidence of microvascular complications. Also, the significant reduction in HbA_{1c} levels that has been detected is expected to independently decrease cardiovascular disease.[18]

When compared to a conventional diabetic diet according to the European Association for the Study of Diabetes (EASD), an equally calorie restricted vegetarian diet led to an increased insulin sensitivity, along with a reduction of visceral and subcutaneous fat and an improvement of oxidative stress.[42]

In this population, achieving low blood pressure levels and optimizing lipid profile is particularly important, to which a vegetarian diet might positively contribute, as explained before.[14]

Oxidative stress and inflammation

Oxidative stress and inflammation play a major role in vascular disorders and circulation defects and contribute to the development of metabolic syndrome. Oxidative stress occurs when there is a disproportion between prooxidants and antioxidants, favouring the first ones.[43]

A low-calorie vegetarian diet adopted for three months by randomly overweight omnivores led to a significant improvement in oxidative stress profile, which supports this potential cardiovascular advantage in vegetarianism.[44] This beneficial effect is most likely related with higher intake of antioxidant compounds such as ascorbic acid, carotenoids and flavonoids that play a protective role against oxidative damage, leading to a lower risk of cardiovascular disease. Additionally, the lipophilic antioxidant vitamin E is known to be an antiatherogenic and anti-inflammatory agent.[45]

Plasma ascorbic acid concentrations have been shown to be nearly 50% higher in a vegetarian population when compared to non-vegetarians. These numbers were inversely correlated with unstable coronary artery disease activity in patients with established cardiovascular disease, as well as cardiovascular disease mortality.[45]

Plasmatic biomarkers concerning oxidative profile and inflammatory status may also help assessing cardiovascular health, and C-reactive protein (CRP) is validated as an independent predictor of cardiovascular disease. A long-term vegetarian diet was found to be associated with lower values of high-sensitivity CRP,[45] but this has not been consistent over the researches developed on the topic. Some studies found no significant disparity in CRP levels between vegetarians and omnivores. This could have happened because vegetarians have reduced intake of other relevant nutritional components such as anti-inflammatory omega-3 (n-3) fatty acids and vitamin D, which may lessen the expected anti-inflammatory effect.[16,30]

New circulating biomarkers have been recently studied to be anticipatory of a higher cardiovascular risk. Elevated concentration and activity of matrix metalloproteinases (MMPs) may predict a greater risk of cardiovascular disorders, specifically MMP-2 and MMP-9. These are inflammation-related biomarkers and have been associated with hypertension-induced cardiovascular remodelling, atherosclerotic mechanism development, and aneurysm related cardiovascular maladaptation. Additionally, myeloperoxidase (MPO) is an important prooxidant enzyme associated with cardiovascular diseases, which role is to produce reactive oxygen species (ROS) when in oxidative stress. In higher concentrations, ROS will cause endothelial dysfunction and arterial remodelling. It has been shown that vegetarian diets are associated with lower concentrations of the above mentioned biomarkers, which can reinforce evidence of a reduced predisposition to cardiovascular events in such population.[11]

Blood viscosity

Blood viscosity may influence cardiovascular health since it plays a role in atherosclerosis, thrombosis and ischemic events. It increases along with haematocrit levels and they both contribute to platelet adhesion and deposition, favouring thrombotic complications. Additionally, there is a positive association between total cholesterol and triglyceride concentrations and blood viscosity, because in elevated amounts they impair erythrocytes' morphology and flow behaviour, which enhances their aggregation.[46]

Increased erythrocyte aggregation and altered blood viscosity have additionally been linked to oxidative stress, as a result of oxidative damage to erythrocytes.[43]

It has already been shown blood fluidity can be increased by adopting a vegetarian diet, most likely by virtue of being a dietary pattern low in saturated fats and total cholesterol and, on the other hand, high in antioxidants.[46]

Intestinal microbiota

Recently, another contributory factor to atherosclerotic mechanism has been studied: trimethylamine (TMA). It is obtained through some dietary compounds of meat, milk, and other animal derived foods, namely lecithin, choline betaine and carnitine, which are converted by intestinal bacterial enzymes into TMA. TMA is posteriorly absorbed and oxidized into a toxic component – trimethylamine N-oxide (TMAO) - which has been shown to enhance oxidized LDL uptake by macrophages in atherosclerosis mechanism. TMAO seems to play a role in promoting atherosclerosis by activating macrophages and foam cells and it is elevated in patients with coronary heart disease.

TMAO's synthesis is an intestinal-microbiota-dependent mechanism, which means conversion into TMA from substrates only happens with enzymes from some specific microorganisms, which may or may not be present in each host's microbiota. Long-term vegetarians, not only do not ingest these substrates usually found in animal food products, but they also lose the ability to produce TMA due to their different microbiota.[9,13,15]

According to this new hypothesis, it is clear why a dietary routine which does not include animal derived items might be advantageous in minimizing atherosclerotic cardiovascular disease.[12]

Concerns

Despite all the benefits shown above regarding this nutritional pattern, a non-balanced vegetarian diet could lead to nutritional deficiencies which could nullify these advantages.[47]

Vitamin B12

The main sources of cobalamin (vitamin B12) intake in general population are animal derived foods, with a significant contribution of dairy products. Recommended dietary intake values vary among authors, ranging between 2.4 to 4 ug per day in adults. With aging, there is a reduction in absorptive capacity and some researchers believe this amount may not be sufficient anymore.[47]

Recent studies report low plasmatic cobalamin concentrations among vegetarian population. This vitamin can, in fact, be found in some plant derived foods, such as mushrooms, seaweeds, fermented soy products like tempeh, but not in consistently relevant amounts. However, the use of supplements or fortified food products are able to prevent deficiencies, indicating that a well-planned vegetarian diet is potentially sustainable.[48,49]

The association between low levels of holo-transcobalamin, the functional available form of vitamin B12, and higher rates of coronary artery disease among vegetarian people has already been demonstrated.[25]

Concerning this cardiovascular impact, it is known that plasmatic homocysteine and cysteine tend to accumulate in vegetarian population due to vitamin B-12 deficiency. A few studies have reported a relationship between raised homocysteine plasmatic levels and increased arterial stiffness, atherogenicity and inflammation, as well as higher likelihood of cardiovascular events.[12,16] More recently, on the other hand, it was cysteine, one of the converted products from homocysteine, that has been linked to coronary artery disease in a vegetarian population study.[25] Additionally, even though it has been shown that vitamin B12 supplementation is able to quickly correct hyperhomocysteinemia, there is no solid proof that it brings a significant positive impact in vegetarians' cardiovascular health.[48]

Besides vitamin B12 deficiency-induced hyperhomocysteinemia, lacking in this vitamin may lead to macrocytosis and increased RDW, which is associated with circulatory problems and a higher rate of cardiovascular events.[48]

Also, a causal relationship between vitamin B12 deficiency and low levels of HDL has been proven and explained by a downregulation of peroxisome proliferator-activated receptor α (PPAR α), which is responsible for HDL's major protein component synthesis, apolipoprotein A1.[25]

There is no unanimity on supplementing vegetarian population. Ovo-lacto-vegetarians can get adequate vitamin B12 from dairy and eggs, but for vegans it must be obtained from fortified

foods or supplements.[50] Therefore, due to risks mentioned above, screening for vitamin B12 deficiency and considering adjusted supplementation should be pondered in a healthy plant-based diet. It is also important to point out that supplementing with multivitamins can actually be counterproductive since cobalamin can be degraded in the presence of vitamin C and copper.[47]

Protein

Protein intake is one of the most popular concerns when someone choses to embrace a vegetarian diet. Protein is made up of smaller units called amino acids, some of which must be obtained from food since they cannot be synthesized by the human body – these are called essential amino acids. Contrarily to popular belief, these special amino acids are not exclusively found in meat, dairy products and eggs. Their intake is also possible through a well-balanced plant-based diet as long as there is a proper combination of food products.[9] Actually, vegetarian diets, including vegan, with an adequate caloric intake usually meet or even exceed recommended protein intake.[51]

Furthermore, vegetarians get protein from different sources than omnivores, which appears to be advantageous to cardiovascular health. As mentioned above, red meat, specially processed meat, has been positively correlated to cardiovascular disease risk.[20]

On the other hand, soy products might have a good impact on lipid profile, blood pressure and insulin resistance,[17,32,39] and protein derived from nuts and seeds carries a protective cardiovascular effect. Nuts hold high amounts of glutamic acid, which has been shown to have lowering blood pressure effects, as well as L-arginine, a precursor of nitric oxide, which is essential to vascular health.[52] In addition, legume plants like peas, lentils and beans are also rich in proteins, folate, iron, potassium, zinc and fibber, nutrients which consumption is inversely related to blood pressure levels. High legumes intake was correlated to a lower cardiovascular mortality.[53]

However, protein and essential amino acids such as leucine, lysine and methionine can be scarce in restrictive vegan diets. This deficiency can lead to a decrease in muscle and lean body mass, since they are necessary for muscle protein synthesis. A decreased lean body mass might be another cause of hyperhomocysteinemia, even in the absence of vitamin B12 deficiency.[54]

Low intake of n-3 fatty acids

We can separate essential polyunsaturated fatty acids (PUFAs) in two subtypes, and we can obtain each one through distinct food groups. On the one hand we have omega-6 (n-6) group – based on linoleic acid – which is largely common, and it is present in seed oils, nuts and

cereals. On the other hand, n-3 fatty acids are based on α-linoleic acid (ALA) and they are essentially in fish oils, with trace amounts in dairy and eggs.[19]

Several studies concluded that a greater intake of long-chained n-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), is associated with lower risk of fatal cardiovascular disease. Accordingly, a reduced intake of EPA and DHA was also associated in previous studies with insulin resistance[40] and enhanced platelet aggregability, which might explain this association.[12] Also, Omega-3 Index, which represents the percentage of EPA and DHA among all fatty acids in red blood cells' membrane, works as an independent predictor of cardiac disease, and it is validated as a representative biomarker of long-term n-3 fatty acid status.[55]

ALA is the most relevant n-3 fatty acid found in plants, and it can be obtained through the ingestion of vegetarian friendly foods like walnuts and soybeans. ALA does not perform the same protective role regarding cardiovascular health as long-chained n-3 PUFAs, namely on lipid profile, blood pressure and inflammation status.[40]

Despite ALA may be endogenously transformed into EPA and DHA, this conversion is very sparse, and it can additionally be inhibited by substrate competition when there is a high n-6: n-3 fatty acid ratio. This is prone to happen in vegetarians because dietary linoleic acid intake in this population tends to be higher than in omnivores.[26]

Even though Omega-3 Index and plasmatic DHA were shown to be significantly lower in vegetarians, this population still shows reduced cardiovascular risk when compared to omnivores, and this changes' impact in overall heart health in this population is yet to be discovered.[12] However, it is possible that cardiovascular risk could be even more reduced by correcting this shortfall.[8,55]

When supplementation with these long-chained n-3 PUFAs was tested in vegetarians, a reduction in platelet aggregation percentage was observed along the raise in plasmatic EPA and DHA. On the contrary, supplementation with ALA seems to be ineffective in increasing conversion to long-chained n-3 PUFAs, so it is probably useless.[12,56]

Nowadays, ESC recommends fish consumption 1-2 times per week, one of which to be oily fish, which would provide around 400-500 mg EPA and DHA a day. For people who do not consume fish, this reference amounts can be reached through fish oil capsules or DHA-rich microalgae. However, guidelines are not universally consensual, and little is still known about what the most cardioprotective supplement dosage would be. Therefore, more investigation should be performed in order to effective supplementation can be prescribed.[14,57]

Even though it was thought a lower w-3: w-6 ratio could be valuable concerning cardiovascular health, positive effects of w-6 fatty acids on total and LDL-cholesterol and blood pressure have

also been proven, as well as on cardiovascular risk reduction. Therefore, adequate intake of both subtypes is important to optimize cardiovascular protection.[38]

Iron

Iron shortage is a very common nutritional disorder, and it can lead to anaemia and interfere with cardiovascular health. It has been shown risk of coronary artery disease rises with iron depletion, independently of concomitant anaemia. Additionally, concerning heart failure patients, it is unequivocally an independent predictor of death.[58]

Meat is usually the biggest contributor regarding iron supply when compared to other food groups. Even though there is a great amount of iron in a plant-based diet, absorption of heme iron, which is abundant in red meat, is better than of non-heme iron found in plant foods.[59]

Notwithstanding, a meta-analysis suggested that heme iron intake may be considered a cardiovascular disease risk factor, while there is no evidence that non-heme iron or total iron consumption presents any correlation.[60]

Furthermore, when haemoglobin concentration and iron deficiency risk are compared between vegetarians and omnivores, there are no significant differences. Vegetarians tend to consume larger amounts of food rich in vitamin C, which improves non-heme iron absorption and nullifies a potential deficiency risk.[9]

Basing on the information that a significant rise in cardiovascular mortality happens with ingestion of heme-iron and red meat, and since there is not a demonstrated increased iron deficiency risk among vegetarians, we believe this is not a major concern in this population forasmuch as a balanced nutritional pattern is carefully followed, including iron and vitamin C sources.[59]

Vitamin D

To produce Calcitriol, the biologically active form of vitamin D, we need UV sun light exposure and dietary vitamin D2 and D3 ingestion. During the winter, when daylight time is shorter and sun rays' intensity and angle are poor, or even as a result of a more indoor lifestyle, vitamin D synthesis via sunlight exposure can be less efficient.[61]

Dietary Vitamin D intake among vegetarians is significantly lower when comparing with omnivores. Plus, it is mainly consumed in the form of Vitamin D2 which is less bioavailable than animal derived Vitamin D3.[9,62]

Vitamin D is very important in calcium and phosphate plasmatic levels adjustment, and it also plays a role in regulating endothelial nitric oxide's synthesis and arterial stiffness. Previous studies showed that a shortage of vitamin D is associated with raised arterial calcification,

inflammation, imbalanced vasoconstriction and vasodilation score and, therefore, an increased cardiovascular risk.[62,63]

However, there have been some discrepancies among results, and higher levels of vitamin D were also associated with raised cardiovascular risk. A study preformed in rats showed a U-shaped dose-response curve between vitamin D levels and systolic blood pressure and arterial stiffness. These results are consistent with the hypothesis that higher levels of vitamin D can also be deleterious towards cardiovascular health.[61]

This means that considering supplementation could be needed, but it must be carefully evaluated in each situation in order that plasmatic levels do not surpass the point where they represent an adverse cardiovascular effect. This threshold, however, is yet to be determined. Plus, it has not been evaluated yet whether the correction of a vitamin D deficiency will have an impact in cardiovascular disease and further research is needed.[61,62]

Healthy *versus* Unhealthy vegetarian diet

It is important to be aware that a vegetarian diet *per se* may have many different approaches. It is possible to follow a vegetarian diet and still ingest great amounts of refined and processed food products, resulting in overconsumption of sugar and trans fats.[64]

Three prospective cohort studies were developed to compare the impact in coronary heart disease development between an overall plant-based diet, a healthy plant-based diet and an unhealthy plant-based diet. This last option included fruit juices, refined grains, potatoes, sugar sweetened beverages and sweets or desserts. They realized that a healthier version of a plant-based diet, which embraced predominantly whole grains, fruits, vegetables, nuts, legumes, vegetable oils, tea and coffee, is in fact inversely associated with coronary heart disease. Contrarily, when intake of less healthy plant foods mentioned above was emphasized, the opposite association was observed, leading to an increased risk.[65]

Whole grain cereals are rich in fiber which makes them advantageous concerning cardiovascular risk, by lowering the risk of insulin resistance, improving lipid profile and facilitating weight control. It also seems to have a positive influence on endothelial function and inflammatory parameters.[3]

It is recommended to increase consumption of fruits and vegetables, at least five servings per day, which has shown improvement in several cardiovascular risk factors such as blood pressure, lipid profile, weight, insulin levels, inflammatory status and endothelial function.[3] A recent meta-analysis came to the conclusion that the lowest risk for cardiovascular disease was observed at an intake of 800 g per day, which rounds about ten servings per day.[66]

A meta-analysis of prospective cohort studies said a daily intake of 30g of nuts diminishes cardiovascular disease risk by 30%, and they are a very good alternative to protein and fatty acids intake. Even though it is crucial to acknowledge that energy density of nuts is high and that a non-rationalized consumption could contribute to overweight, it has unexpectedly been found an inverse association between nut consumption and body weight, BMI and waist circumference. Legumes are also a great source of vegetable protein, which may help improving blood cholesterol and controlling body weight.[14,20,67]

A recent review took the nation with the largest percentage of vegetarians as an example, the Indian population, to show how nutritional changes within a meatless diet might have an impact in cardiovascular health. Even though vegetarianism popularity remained unchanged, a substantial increase in the prevalence of diabetes, obesity, coronary heart disease and stroke has been noticed, and it might have as an underlying cause a dietary switch, in which whole plant foods are being replaced by refined carbohydrates and packaged, processed, fried foods.[68]

In contrast to natural vegetarian food items like fruits, vegetables and whole grains, refined grains and carbohydrates and processed foods such as white rice, fried snacks, or sugar added products like sugar-sweetened beverages, often increase the risk of type 2 diabetes.[38]

The trans fatty acids are a subtype of unsaturated fats that have been shown to be particularly harmful to cardiovascular health, and they can be naturally found in meat and milk of ruminant animals or be synthetized during fats industrial processing. Therefore, they can still be found in vegetarian diets for example in margarine, fast-food and bakery products and packaged fried snacks, and have an impact by increasing total cholesterol, LDL-C, apolipoprotein B, triglycerides, and decreasing HDL-C and apolipoprotein A1.

On average, a 2% increase in energy intake from trans fats increase cardiovascular disease risk by 23%. It is recommended that less than 1% of total energy intake derives from trans fatty acids, considering that the less the better. Hence, these unnatural food products intake should also be discouraged within a vegetarian diet.[14,19]

Processed food also contributes to about 80% of salt intake, which should not overpass 5 g per day according to recommendations. Salt reduction is an important strategy to prevent coronary artery disease, which is an additional motive to reduce these products' intake.[14]

Discussion

Overall, several independent mechanisms may explain the beneficial cardiovascular effects of vegetarian diet.

It has been shown a very positive impact on lipid pattern, specially by lowering total cholesterol, LDL-C and apolipoprotein-B,[16,17] even though HDL-C and triglycerides results are not consensual. In some studies, vegetarians were prone to lower plasmatic HDL-C, which could be an adverse factor concerning cardiovascular risk, while on others there was no significant difference.[17] Either way, having a low HDL due to reduced fat intake, which is probably the reason behind this tendency in this population, is not associated with worse cardiovascular health.[10] Plus, TC:HDL ratio, which represents a strong piece in cardiovascular risk assessment, remains lower.[26] Triglyceride levels among vegetarians ended up creating a controversy, and while in some of them a higher number of plasmatic triglycerides was achieved, this can possibly be attributed to higher ingestion of refined carbohydrates, fructose or saturated fats, which can be adjusted through careful evaluation and planning of a vegetarian nutritional plan.[10] Recent findings regarding chylomicron remnants, a triglyceride-rich lipoprotein, revealed another atherosclerosis protective mechanism attributed to vegetarianism. Chylomicron remnants were shown to be are potentially atherogenic when accumulated, and their removal from the circulation seems to be done more efficiently among vegetarians.[27]

BMI and waist circumference have both been shown to be significantly lower in vegetarians when compared to non-vegetarians.[10,30] Also, as an intervention strategy, several vegetarian diets, namely a low-fat one even without calorie restriction or mandatory regular exercise, have been shown to lead to a significant BMI and weight reduction in an either overweight and obese population.

A vegetarian diet is a good nutritional choice one can make to reach a better blood pressure control,[32] which could be associated to a lower BMI,[33] higher intake of potassium,[10] and also increased dietary nitrate that is mainly present in vegetables.[33] Additionally, higher consumption of protein from plant sources while taking animal protein out seems to be advantageous towards blood pressure management.[32,34]

It has been shown that vegetarianism is able to lead to a 50% reduction in risk of diabetes and changing to a totally plant-based diet improves glycaemic control in weeks. Beyond BMI reduction, which brings better glycaemic control and insulin sensitivity,[38,39] great amounts of fibre, plant polyphenols, soy products and magnesium seem to play a role in this major risk factor.[39,40] Additionally, meat is rich in saturated fats that trigger human B-cell apoptosis, which are responsible for insulin secretion,[39] and fatty acids specifically held in meat are negatively associated with insulin's secretion and sensitivity.[41] Opting for a vegetarian diet also seems to

provide a better glycaemic control in diabetic people, which is essential to reduce the incidence of microvascular complications. This means it could be used beyond prevention, but also as a therapeutic weapon in this chronic disease.[18]

In some studies, a plant-based diet also showed a beneficial effect on new oxidative stress and inflammation biomarkers, such as MMP-2, MMP-9 and MPO. This positive impact is most likely due to higher intake of antioxidants like ascorbic acid, vitamin E, carotenoids and flavonoids, which grant a protective role against oxidative damage, and consequently vascular disorders, circulation defects and cardiovascular disease.[45] However, a reduced intake of anti-inflammatory n-3 fatty acids and vitamin D might lessen the expected anti-inflammatory effect.[11,16,30]

Blood viscosity, which plays a role in atherosclerotic, thrombotic and ischemic events, can also be decreased by adopting vegetarian diet, most likely for being low in saturated fats and total cholesterol, and yet high in antioxidants.[46]

As a promoter of atherosclerotic mechanism, a new intestinal-microbiota-dependent toxic component was recently discovered - trimethylamine N-oxide (TMAO). If on the one hand, it is only converted from dietary compounds like meat, milk, and other animal derived foods, on the other hand long-term vegetarians also lose the ability to produce this toxic component due to changes in their microbiota.[9,13,15] Thus, by this two different paths, vegetarian population is protected from this atherosclerotic trigger.[12]

Some concerns have been raised concerning these dietary patterns since certain nutrients may be less available when excluding animal products, even though there are considerable variations depending on the specific dietary choice.[18] The most pertinent concerns related to cardiovascular disease include vitamin B12, essential amino acids, specific types of fatty acids, vitamin D and iron.

The main source of vitamin B12 intake in general population is indeed animal derived foods, with a significant contribution from dairy products,[47] and recent studies report low plasmatic cobalamin levels among vegetarian population. Low levels of this vitamin can lead to accumulation of homocysteine and cysteine, and macrocytosis, which increase the risk of coronary artery disease and circulation problems.[16,25,48] Even though it is still not clear if it actually brings a positive impact on cardiovascular health, the use of supplements or fortified food products are able to prevent this deficiency, indicating that an individually well-planned vegetarian diet can be sustainable.[48,49]

A balanced plant-based diet with a proper combination of food products is able to supply all essential amino acids and recommended protein intake.[9,51] Additionally, meat protein has been positively correlated to greater cardiovascular risk, while soy, nuts and legumes protein carry a protective effect.[17,52,53]

Long-chained n-3 fatty acids are essentially present in fish oils, with trace amounts in dairy and eggs, and their intake has shown positive impact on cardiovascular disease reduction.[19] Despite these fatty acids were significantly reduced in vegetarians, this population still shows lower cardiovascular risk when compared to omnivores, and this setting's impact in overall heart health of this population is yet to be discovered.[12] It is possible that cardiovascular risk in vegetarians could be even lower by correcting this shortfall.[8,55]

Iron shortage is a common nutritional disorder, and it can promote anaemia and coronary artery disease, but there is no evidence that it is more frequent in vegetarians.[9,58] Meat is usually the biggest iron supplier because even though there is a good amount of it in a plant-based diet, absorption of heme iron found in red meat is more efficient than non-heme iron from plant foods.[59] Yet, heme iron might be considered a cardiovascular disease risk factor, while there is no evidence that non-heme iron or total iron consumption presents any correlation.[60]

Dietary vitamin D is present in vegetarian food products in lower amounts and it is less bioavailable.[9,62] This vitamin plays a role in regulating endothelial nitric oxide synthase and arterial stiffness and calcification, and its shortage is associated with cardiovascular disease.[62,63] However higher levels of vitamin D can also be deleterious towards cardiovascular health.[61] This means considering supplementation might be needed when deficiency is present, but it must be carefully evaluated. There is also no certainty that correction of vitamin D deficiency will have an impact in cardiovascular disease.[61,62]

In the end, a vegetarian diet can be advantageous towards cardiovascular disease prevention and management. It ameliorates several already known risk factors as well as new alternative pathways that lead to atherosclerosis and other circulatory issues. Nonetheless, it is essential to be appropriately planned and nutritionally adequate, in order to supply certain nutrients that can be more difficult to acquire through plant-based products. In some cases, specific food combinations or even supplements may be required to get all macro and micronutrients. Additionally, a vegetarian diet might be followed in an unhealthy approach, with a great ingestion of refined and processed food products. This overconsumption of sugar and trans fats brings a strong negative impact in cardiovascular health, nullifying the positive aspects of a vegetarian diet. Thus, it must be avoided. For that matter, health care providers should be aware of all types of vegetarian diets and their risks and benefits regarding cardiovascular disease, since with proper guidance and planning it can be used as a therapeutic weapon.[18,64]

Conclusion

Cardiovascular disease is a leading cause of morbimortality which makes it crucial to find new prevention and management strategies.

We realized through this review that following a vegetarian diet brings a beneficial effect in several independent cardiovascular risk factors. Recent studies on the topic keep on finding new mechanisms through which such positive impact is made.

Even though there are some challenges in reaching specific macro and micronutrients which are less available in plant-based foods, their insufficiency can usually be avoided by planning a well-balanced and complete diet, built with healthy and natural food components.

Overall, even despite some potential deficiencies, vegetarian population showed a reduced cardiovascular risk. Therefore, a vegetarian diet can represent an effective therapeutic approach concerning cardiovascular risk reduction, considering there is the awareness of its potential limitations and corresponding precautions are taken.

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