fortune Journals

Review Article

CARDIOLOGY AND CARDIOVASCULAR MEDICINE

ISSN: 2572-9292

Mechanisms Plant-Based Diets Reverse Atherosclerosis

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Abstract

Atherosclerosis, a chronic systemic inflammatory process, is the leading cause of disease, disability, and mortality worldwide. While current management approaches can temporarily alleviate the problem, they do not address the root cause. This paper presents a novel approach, demonstrating that adopting a whole food plant-based diet (PBD) can reduce the risk of atherosclerosis-related conditions and cause atherosclerosis to regress. We will delve into the mechanisms by which PBDs can cause regression of atherosclerosis plaque, a crucial aspect in managing coronary artery disease (CAD) patients. Despite the significant role of PBDs in managing CAD, the medical community has been slow to embrace this approach. By providing more information on the mechanism of action of PBDs, we aim to bridge the gap in knowledge and promote wider acceptance and implementation of PBDs by medical professionals.

Keywords: Plant-based diet; Lifestyle; Atherosclerosis; Chronic inflammatory metabolic diseases

Introduction

Atherosclerosis remains the primary cause of illness, disability, and mortality in Indonesia and worldwide [1-4]. While medical advancements have been made, progress is still inadequate, as millions of individuals continue to suffer from atherosclerotic complications despite the use of current treatments. Current practices primarily focus on curative measures, using medications and procedures to treat atherosclerosis rather than focusing on promotive and preventive strategies [5,6].

Atherosclerosis is commonly linked to several well-known risk factors for CAD, including hyperlipidemia, hypertension, cigarette smoking, hyperglycemia, hyperinsulinemia, sedentary lifestyle, and obesity. However, it is crucial to consider the underlying chronic inflammatory conditions that may contribute to the development of these risk factors. Effectively managing these conditions can be accomplished through lifestyle modifications, with adopting a PBD being the most critical approach. In fact, lifestyle factors account for more than 80% of the risk factors associated with atherosclerosis [6], with diet being a significant determinant of the disease [7]. Recommendations for treating atherosclerosis must include lifestyle changes [8-10], but it has been observed that these modifications are not consistently implemented in clinical practice. Numerous factors contribute to this issue; however, the primary reason is the lack of nutritional knowledge among practitioners, which prevents them from making necessary dietary adjustments and the brief duration of their consultations [11].

Several studies have highlighted the crucial role of PBDs in managing chronic inflammatory diseases, including atherosclerosis, hyperlipidemia,

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Citation: Dasaad Mulijono, Albert M Hutapea, I Nyoman E Lister, Mondastri K Sudaryo, Helwiah Umniyati. Mechanisms Plant-Based Diets Reverse Atherosclerosis. Cardiology and Cardiovascular Medicine. 8 (2024): 290-302.

Received: June 20, 2024
Accepted: June 25, 2024
Published: July 04, 2024

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2024 DOI:10.26502/fccm.92920390

obesity, non-insulin-dependent diabetes mellitus (NIDDM), and hypertension. It is widely acknowledged that PBD may not only contribute to the prevention of atherosclerosis but may also cause regression of coronary plaques that have occurred. The role of PBDs as an anti-inflammatory, immunomodulatory, and assisting vascular healing, which contributes to plaque regression, has been well studied and published [12-18]. Furthermore, consuming PBD in conjunction with anti-platelet drugs may aid in mitigating thrombosis processes, potentially reducing the risk of developing acute coronary syndrome (ACS) [19-21]. This is particularly relevant for the management of patients with CAD and stroke, as it can help prevent acute events that may be detrimental, leading to disability or even fatality.

A notable shift has transpired in the management of CAD patients, with the majority of cases now classified as chronic coronary syndrome (CCS), formerly known as stable angina. In the past, patients with CCS were typically treated invasively through the insertion of stents or coronary artery bypass graft (CABG) surgery to address coronary atherosclerosis lesions. However, recent multi-center studies have reached a consensus that, for individuals with CCS, long-term treatment with intensive/optimal medical therapy (OMT), including lifestyle modifications, yields comparable cardiovascular outcomes to percutaneous coronary intervention (PCI) plus OMT [22-24]. Cardiologists who only rely on interventions like stent implantation to treat systemic diseases may not be adequate if they neglect to address their patient's systemic issues. Given that CAD is a systemic chronic inflammatory disease, it is essential to address the underlying systemic issues instead of focusing solely on local stenoses. In addition, using stents presents the potential risks of in-stent restenosis (ISR) and stent thrombosis (ST), necessitating careful consideration before determining the most appropriate and secure treatment option for patients with CCS.

Our cardiac center at Bethsaida Hospital in Indonesia conducted PBD studies added on the OMT on a few hundred CCS patients with intermediate coronary stenosis (40-70%) diagnosed using coronary artery calcium (CAC) and computed tomography coronary angiography (CTCA). All patients declined coronary angiography. After three years of follow-up, all patients exhibited significant regression in their CAC and CTCA findings. No patients were admitted for coronary events during the study. Our findings suggest that PBD intervention can regress atherosclerotic plaque and prevent patients from experiencing ACS.

Our goal is to bridge the gap in knowledge regarding the mechanisms by which PBD can cause atherosclerotic plaque regression. We aim to elucidate how PBD can correct metabolic abnormalities, restore endothelial function, reduce systemic inflammation, enhance the availability of nitric oxide (NO), foster healthy microbiota, correct mitochondrial dysfunction, and improve telomere as part of epigenetic adjustments [25-29]. We believe that PBD is an effective treatment for patients with metabolic abnormalities, can reduce their chronic systemic inflammation, and promote the regression of atherosclerotic plaque, along with its associated contributing risk factors such as obesity, hypertension, hyperlipidemia, glucose intolerance, and thromboembolism.

Based on the positive results that our cardiac center has attained, coupled with the previous studies that have demonstrated the role of PBDs in reversing atherosclerosis [30-32], we propose that all medical professionals should seriously consider incorporating lifestyle modifications into their patient care. These methods are not only effective but also safe and affordable, making them an ideal solution for many health practitioners to adopt. By doing so, we can significantly improve the quality of life and longevity of our patients while also reducing future healthcare costs during these uncertain economic times.

Mechanism PBD in regressing atherosclerosis

The most important mechanism of how PBD regresses atherosclerosis

Atherosclerosis can be prevented by adopting a PBD diet and eliminating consuming foods that contribute to its development. Consuming sugary products, processed snacks, processed meats, red meats, poultry, dairy products, and eggs as part of an omnivorous dietary behavior increases the risk of developing atherosclerosis. These unhealthy eating habits have been linked to several risk factors for atherosclerosis, including dyslipidemia, insulin resistance, hypertension, glucose intolerance, endothelial dysfunction, systemic chronic inflammation, increased oxidative stress, elevated trimethylamine N-oxide (TMAO), low NO, gut dysbiosis, mitochondrial damage, and shortened telomeres (which accelerate the aging process) [25-29]. These factors are widely recognized as risk factors for the development of atherosclerosis.

Mechanism of NO in regressing atherosclerosis

The endothelium exhibits anti-atherosclerotic properties, which can be ascribed to the presence of NO. NO prevents monocytes and leukocytes from adhering to the endothelium, inhibits platelet-vessel wall interactions, and suppresses the proliferation of vascular smooth muscle cells (VSMC), which are important processes in developing atherosclerosis. Additionally, NO promotes coronary dilation and increases coronary blood flow [33]. Furthermore, NO plays a vital role in endothelial regeneration, which is crucial for the healing of the coronary artery to return to its normal anatomy and function [33].

Chronic inflammatory diseases, including obesity, hypertension, hyperlipidemia, insulin resistance, and glucose intolerance, recognized as risk factors for atherosclerosis, can decrease NO release into the coronary wall due to impaired

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synthesis or excessive degradation [34]. PBD has been shown to improve chronic inflammatory diseases and potentially reverse atherosclerosis [12-18]. It is worth noting that NO production decreases with age, as atherosclerosis primarily affects older populations [35]. Currently, NO levels can be measured accurately using a salivary strip, which has a 96% accuracy rate [36].

We can enhance our patients' NO availability by altering their diet and lifestyle. The process of converting nitrate-rich foods, such as green leafy vegetables, into NO is illustrated in Figure 1. Please note that it is crucial to consider that certain vegetables that are high in nitrates can have their nitrate levels reduced through cooking. Food preparation is also a significant factor in determining the effectiveness or beneficial effects of the food [37]. Most studies on PBDs have not adequately assessed the quality of the food consumed by their participants, specifically regarding the selection, quantity, and processing of food items, particularly raw vegetables. This lack of attention may fail to maximize the benefits of PBDs. Another important factor is the potential deficiency of certain vitamins, minerals, and micronutrients often present in people who follow PBDs. Therefore, it is crucial to ensure that these important nutrients are adequately supplemented, as a deficiency in these nutrients may not only decrease the efficacy of a PBD but can also be potentially harmful [38,39].

PBD as an anti-inflammation, antioxidant, and a crucial factor in repairing endothelial dysfunction

In 1998, Ornish et al. conducted a small randomized controlled trial, the Lifestyle Heart Trial. The study demonstrated that intensive lifestyle changes with PBD could reverse coronary atherosclerosis. The most important mechanism of this process is repairing endothelial dysfunction [30]. In 2014, Esselstyn et al. presented a famous image in Figure 2, illustrating that strict PBD can regress coronary stenosis [31].

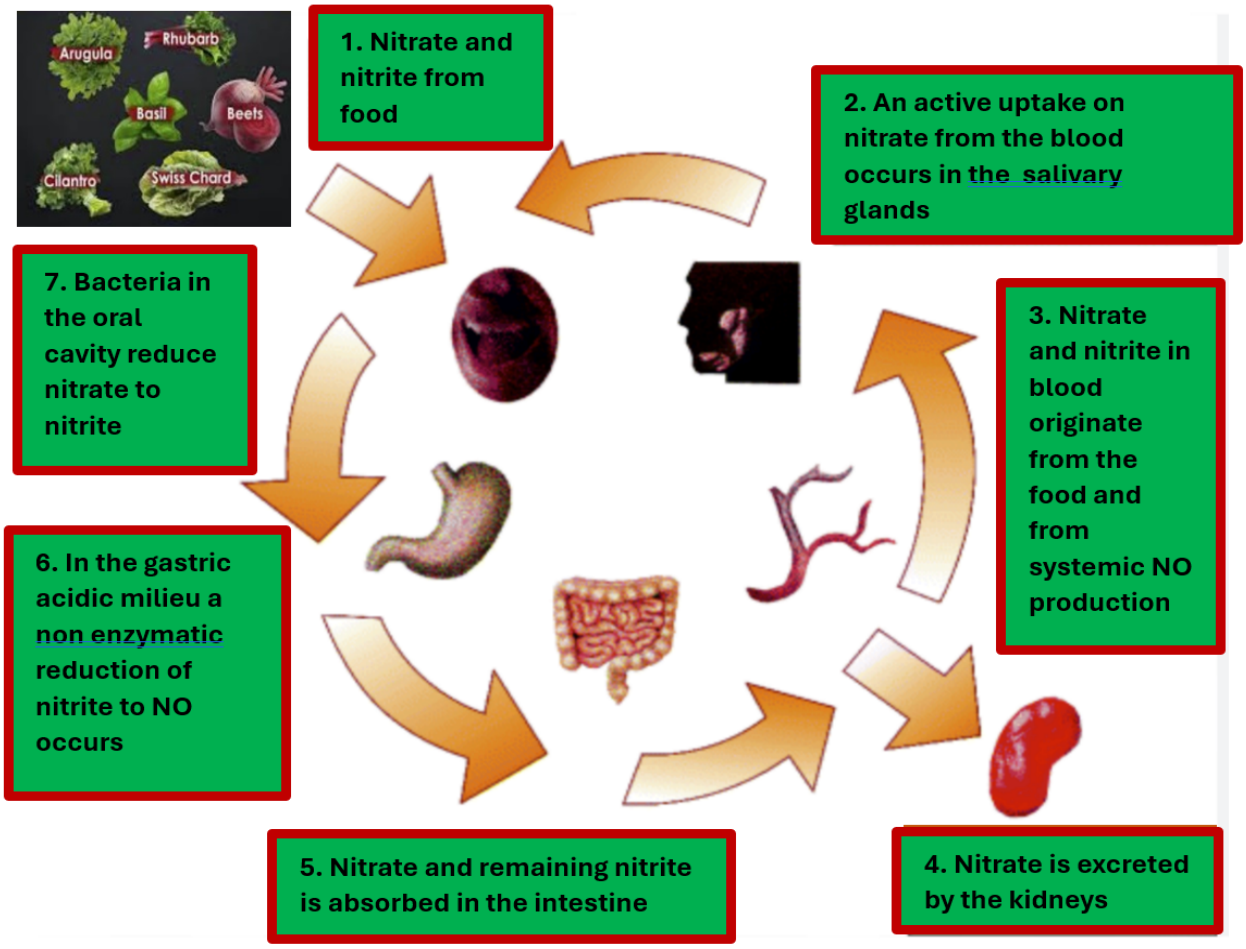

Figure 1: The entero-salivary circulation of nitrate in human

Strategies involving NO can also be crucial in reducing platelet activation and aggregation, thereby decreasing the likelihood of developing ACS. It is crucial to consider NO for the regression of atherosclerosis, stabilization of vulnerable plaque, and decrease of the likelihood of coronary events.

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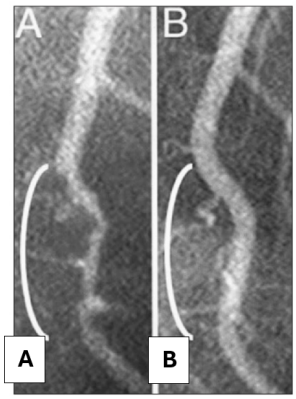

Figure 1 Reversal of coronary artery disease
Coronary angiographically reveals A→ a stenosis 80-90% in the mid left anterior descending artery (LAD), B→ after 32 months of a plant-based intervention, the stenosis became normal (0%).

It has been a decade since the remarkable research studies on atherosclerosis have garnered significant praise and acceptance within the PBD community and among practitioners who recommend PBD. Despite this, the widespread adoption of recommending PBD to patients has not been extensively embraced within the cardiology community. As an interventional cardiologist, I initially had reservations about these findings; however, after being diagnosed with coronary stenosis on my CTCA, I decided to follow the advice of these PBD experts. To my surprise, after three years, my LAD stenosis of 50% had regressed to 30%, and my CT calcium reading had decreased by 30% [40].

Eating poor-quality food that is high in sugar (refined carbohydrate), devoid of fiber-phytonutrients, highly processed, and contains saturated and trans fats, cholesterol, and chemicals that promote chronic inflammation is a major contributor to the development of atherosclerosis. The consumption of these unhealthy foods has been demonstrated to increase levels of LDL cholesterol, triglycerides, apolipoprotein (a), apolipoprotein (b), C-reactive protein (CRP), pro-inflammatory mediators, pro-inflammatory chemokines/ cytokines, TMAO, advanced glycation end products (AGEs), insulin-like growth factor 1 (IGF-1), endotoxins, N-glycolylneuraminic acid (NEU5GC), chemicals (pesticides and pollutants), oxidative stress, tumor promotion, and cell proliferation, among other factors. All of these factors play a significant role in atherosclerosis development [41,42]. On the contrary, eating healthy PBD with adequate supplementations (most commonly vitamins B12 and D and minerals) will enhance our body to fight against inflammation. Healthy foods such as vegetables, fruits, and legumes contain carotenoids, isoflavones, phytoestrogens, and phytosterols, which have been shown to prevent atherosclerosis. Polyphenols and phytochemicals have been shown to play a critical role in molecular signaling, specifically in anti-inflammatory and antiplatelet aggregation, inhibition of VSMCs proliferation and migration, and protection against lipid oxidation (ox-LDL) [43,44]. Atherosclerosis is a known condition involving these factors, namely inflammation, platelet aggregation, VSMC proliferation and migration, and oxidized low-density lipoprotein (LDL).

The formation of an excessive amount of reactive oxygen species (ROS) results in oxidative stress, a significant contributing factor to the emergence and progression of atherosclerosis [45]. Robust evidence indicates that ROS, through their pro-atherogenic effects, play a crucial role in several pathological processes, including inflammation, endothelial dysfunction, and dysregulated lipid metabolism. Moreover, ROS has been demonstrated to impair mitochondrial function, which is critical to ensure effective healing of the coronary arteries. Overproduction of ROS leads to platelet dysfunction and subsequent abnormal activation and aggregation, which can contribute to the formation of blood clots, subsequently causing an ACS [46].

Carotenoids, prominently present in foods like pumpkin, carrots, tomatoes, green leafy vegetables, broccoli, and bell peppers, are lipophilic antioxidants that can mitigate the detrimental effects of ROS. Citrus fruits, bell peppers, strawberries, kiwis, broccoli, green leafy vegetables, grains, and legumes are rich in vitamin C and the B-complex group. Both vitamins function as potent antioxidants, helping combat ROS's negative effects. Thus, adopting healthy dietary habits in conjunction with PBD can guard against the onset of atherosclerosis. It is important to note that individuals who have adopted healthy and correct PBDs may never develop coronary atherosclerosis in their lives so that coronary intervention can be avoided in their lifetimes. Consuming foods that decrease the dietary inflammatory index (DII) is advisable to counteract the inflammation and ROS implications in the progression of atherosclerosis, as depicted in Table 1.

Table 1: List of foods that increase and decrease DII

Foods that increase DII	Foods that decrease DII
Red meat (steak and hamburgers)	Plant-based proteins (beans, lentils, chickpeas, edamame, hemp seeds, tofu, tempeh, and nuts)
Animal products (including eggs and dairy products)	Whole grains (oatmeal, buckwheat, quinoa, pigmented rice)
Processed meat	Starchy vegetables (sweet potatoes and beets)
Commercial baked goods	Seeds (flaxseeds and chia seeds)
White flour (bread and noodles), white rice	Green leafy vegetables (raw)
Deep-fried foods	Colorful vegetables (raw)
Sugary products	Fruits (berries, apples, grapes, oranges, peaches, figs, bananas, and kiwi)
Products with trans-fats	Spices and herbs (turmeric, ginger, cumin, peppermint, cinnamon, chili, parsley, bay leaf, and basil)
Saturated fats (especially animal fats)	
Cholesterol (red meats, processed meats, eggs, fried foods and dairy products)	

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The connection between microbiota and atherosclerosis

The gut microbiota is a complex community of microorganisms that inhabit the gastrointestinal tract and play a crucial role in regulating various physiological processes, including metabolism, inflammation, and immunity. Recent research has revealed that the bacteria in atherosclerotic plaques share DNA similarities with gut bacteria. One of the metabolites produced by the gut microbiota, TMAO, is primarily derived from dietary sources such as choline, betaine, and L-carnitine found in an omnivorous diet. TMAO has been linked to the development and progression of atherosclerosis due to its pro-inflammatory properties and inhibition of reverse cholesterol transport. Additionally, elevated levels of plasma TMAO have been associated with ruptured plaque and thrombosis, which may contribute to ACS [47,48]. With a high intake of red meat, Omnivore's risk for developing atherosclerosis is much higher compared to those who consume PBDs [12]. Switching to a PBD may protect against atherosclerosis by promoting endothelial protective mechanisms and lowering TMAO, a pro-atherosclerotic metabolite.

Atherosclerosis patients commonly display heightened levels of microbiomes that produce TMAO and reduced populations of microbiomes that produce short-chain fatty acids (SCFAs). SCFAs, a type of anti-inflammatory metabolite, are generated through the consumption of a fiber-rich diet. By increasing the expression of anti-inflammatory factors, bolstering the integrity of the intestinal barrier, and suppressing pro-inflammatory cytokines, SCFAs help mitigate inflammation, which is a significant risk factor for atherosclerosis. An imbalance between SCFAs and TMAOs can promote inflammation and intensify the likelihood of developing atherosclerosis.

PBD followers have been shown to possess a microbiome capable of producing significant SCFAs, including butyrate, and increased Acetyl-CoA and X4-aminobutyrate-succinate pathways. Additionally, PBDs have been linked to a lowered post-prandial glycemic response (PPGR), lowered inflammatory markers, improved cardio-metabolic health, low T-cell repertoire diversity, and low IgE expression levels. These beneficial microbiome characteristics may help protect against the development of atherosclerosis and other chronic inflammatory conditions like obesity, hypertension, hyperlipidemia, glucose intolerance, and insulin resistance.

Changes in gut microbiota have the potential to impact gut permeability, which can lead to the translocation of bacterial DNA, lipopolysaccharides (LPS), and proinflammatory cytokines into circulation. This phenomenon, known as leaky gut syndrome, can result in the absorption of metabolites and endotoxins into the bloodstream. Leaky gut syndrome has been linked to the development of atherosclerosis and ACS [49]. SCFAs can reduce gut permeability by decreasing nuclear factor-kappa B (NF-kB) activation and reducing proinflammatory cytokines such as interleukin-1b (IL-1b), IL-6, IL-8, and tumor necrosis factor-alpha (TNF-α) [50]. Low consumption of plant-based foods may lead to increased penetration of the intestinal barrier, as a low-fiber diet triggers a shift from fiber-degrading to mucus-degrading bacteria. This could promote a hyperactive immune response, conceivably with the production of pro-inflammatory metabolites that fuel the disease process.

A healthy diet includes non-digestible carbohydrates, such as resistant starch, soluble and insoluble dietary fiber, and plant wall polysaccharides and oligosaccharides, fermented by beneficial gut bacteria to produce butyrate and other SCFAs. These SCFAs possess anti-inflammatory properties and can strengthen the intestinal barrier, thereby promoting optimal gut health. Moreover, SCFAs can inhibit the formation of foam cells by stimulating the expression of IL-10 and decreasing the production of pro-inflammatory cytokines by the endothelium. This contributes to the endothelial healing and regression of atherosclerosis [51].

Foods high in fiber, including barley, wheat bran, brown rice, and other whole grains, legumes, fruits, and vegetables, as well as prebiotics like fructo-oligosaccharides, are commonly consumed by individuals following a PBD diet. Plant-based foods also contain polyphenols such as lignans, isoflavones, anthocyanins, and flavonols, as well as other phytochemicals like carotenoids and phytosterols, which are metabolized into bioactive compounds by beneficial microbes, conferring health benefits and exhibiting anti-inflammatory and antioxidant activity. Phytochemicals have been shown to increase the populations of beneficial bacteria such as Lactobacillus and Bifidobacterium, which are the primary species found in probiotic supplements that are taken to improve gut health. In addition, fiber-rich plant foods like nuts such as walnuts, almonds, and pistachios have been found to have prebiotic effects, leading to increases in butyrate-producing microbes and other beneficial microbes. Overall, the composition of the gut microbiome is greatly influenced by dietary fiber, polyphenols, and other phytochemicals and their metabolites, consumed in greater quantities by those following PBDs [52]. Certainly, a diet that is low in fiber, devoid of polyphenols and phytochemicals, and deficient in SCFAs while being high in TMAO may contribute to the development and progression of new atherosclerotic plaques. A significant relationship exists between the gut and the heart, commonly called the gut-heart axis [53,54], as illustrated in Figure 3.

Caloric restriction (CR) is an essential factor in combating inflammation

In 2022, 43% of adults aged 18 years or older were considered overweight, and 16% were diagnosed with obesity [54]. Overeating is a pervasive issue in contemporary society, influenced by various factors, including the availability of

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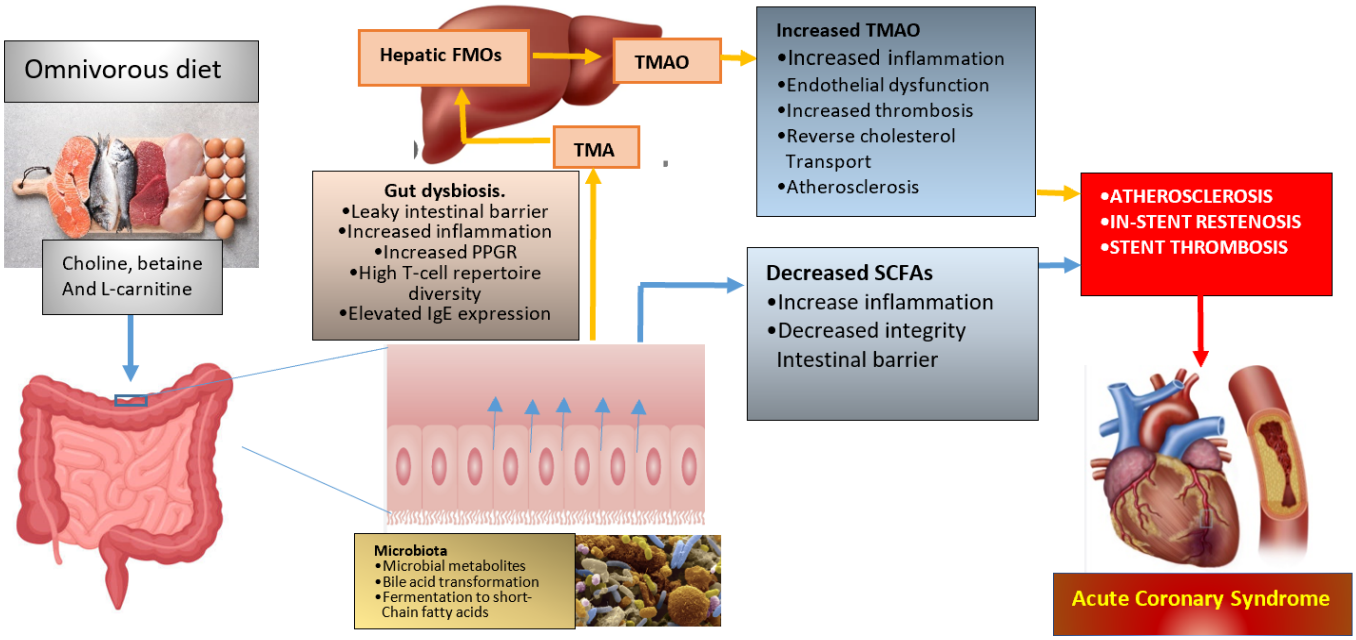

Figure 3: The gut-heart axis, in which diet affects the development of atherosclerosis, ISR and ST through gut microbiota

copious amounts of food, stress, emotional eating, and social tradition. While partaking in occasional feasts is an ingrained aspect of human nature, persistent overeating can severely affect an individual's health and society. Upon evaluating a substantial number of individuals who have attended our cardiology clinic, we have determined that a substantial proportion, exceeding 90%, would be classified as overweight using the BMI threshold of 21 kg/m2 from healthy PBD eaters. This finding is not surprising, given the prevalence of CAD among this group. Our clinic offers a lifestyle program to help patients maintain their ideal weight by restricting their calorie intake.

CR, which involves reducing the intake of calories without depriving essential nutrients, has consistently demonstrated anti-aging effects across various organisms. Furthermore, it has been shown to protect against age-related diseases such as cardiovascular disease, NIDDM, hypertension, hypercholesterolemia, and cancer. CR has been shown to positively impact patients' metabolic parameters by decreasing oxidative stress and inflammation while simultaneously promoting the production and activity of antioxidant and anti-inflammatory compounds. This ultimately leads to a more balanced state within the body. Studies have also shown that CR can improve overall health and well-being, optimize energy metabolism, enhance cellular protection, improve insulin sensitivity and glucose regulation, induce functional changes in the neuroendocrine systems, reduce oxidative damage and inflammation, and even shape the gut microbiota [56].

Implementing CR may improve cardiovascular health. By promoting the activity of endothelial NO synthase (eNOS) and sirtuin 1 (SIRT1), CR can enhance endothelial function, leading to vasodilation, regulation of blood pressure, and improved blood flow. Additionally, CR may also reduce the development of atherosclerosis [57]. Eating an unhealthy diet with calorie excess will certainly promote the development and progression of atherosclerosis [58]. CR protects DNA methylation, histone modification, and non-coding RNA (nc-RNA), which prevent VSMC proliferation, migration, and inflammation, which play an important role in developing atherosclerosis [59,60]. The majority of individuals who adhere to PBDs typically do not require engaging in CR, as these diets naturally foster feelings of fullness and satisfaction. Additionally, the majority of items on PBD menus are low in calories. In stark contrast, most omnivorous individuals frequently experience feelings of hunger due to the malfunctioning of their hormonal regulators, typically caused by consuming unhealthy foods with minimal nutrients and empty calories. Hence, our investigation indicates that CR may lead to atherosclerotic plaque regression, attributed to its various beneficial effects via multiple mechanisms.

The role of PBD as mitochondrial protectors

As we age, the powerhouses of our cells, called mitochondria, undergo changes that lead to a decline in their function. This decline is caused by the accumulation of oxidative damage and mutations that induce ROS. As a result, the volume, integrity, and functionality of mitochondrial DNA (mtDNA) decrease. In older adults, mitochondria are characterized by significant increases in ROS and decreased antioxidant defense, which lead to impaired functions. These include decreased ATP production, lowered oxidative capacity, and reduced oxidative phosphorylation [61].

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Additionally, with aging, mitochondrial biogenesis will decline due to inhibition of mitophagy and alterations in mitochondrial dynamics (fission and fusion). Mitophagy, an autophagy process that eliminates defective mitochondria, also deteriorates with aging. An excessive generation of ROS characterizes acute and chronic inflammatory diseases, which can cause damage to mtDNA, mitochondrial proteins, and lipids. This negatively affects normal mitochondrial function and dynamics, contributing to atherosclerosis development. Inflammation is generated by various mitochondrial products called damage-associated molecular patterns (DAMPs) and is released into the cytosol or extracellular environment. Protective measures are in place to prevent mitochondria from triggering harmful inflammatory responses, such as disposing of damaged mitochondria through mitophagy. However, if these mechanisms are overwhelmed or not functioning correctly, inflammatory reactions instigated by mitochondria can become problematic, contribute to developing disorders, and impede healing [62].

Mitochondria are of paramount significance for the functioning of cellular metabolism, the production of energy, and the survival of cells. Atherosclerosis, a disease of the arterial wall, can also be caused by the malfunction of mitochondria, which results in the accumulation of lipids, elevated levels of ROS, chronic inflammation, and oxidative stress. These factors can harm endothelial cells, which may trigger the development of atherosclerosis. Vascular endothelial cells play a crucial role in regulating apoptosis and NO production. They are also important in modulating cell signaling and the cellular response to stress, which this type of cell is particularly sensitive to. In addition to their barrier function, endothelial cells are involved in regulating vascular tone, the transport of blood plasma molecules, hemostasis, inflammation, and lipid metabolism. A healthy endothelial barrier prevents the infiltration of circulating cells, such as monocytes/macrophages, into the vascular wall. Endothelial dysfunction is one of the earliest signs of mitochondrial disorder [63]. Furthermore, mitochondrial dysfunction can also threaten other cells in the arterial wall, such as VSMCs, macrophages, monocytes, and lymphocytes. The malfunction of mitochondria is a critical factor in developing chronic inflammatory diseases, including hypertension, obesity, hyperlipidemia, NIDDM, and obesity. The chronic inflammation process will cause mitochondrial dysfunction, and conversely, mitochondrial dysfunction will exacerbate the chronic inflammation process. All of these mechanisms are of utmost importance in the pathogenesis of atherosclerosis [64].

ROS plays a pivotal role in damaging mtDNA, decreasing the amount of coding mtDNA, impairing mitochondrial protein synthesis, altering mitochondrial membrane potential, and decreasing total ATP production in endothelial cells and VSMCs. These factors are crucial in the development of atherosclerosis. Changes in the mitochondrial genome, such as an increase in mtDNA copy number, mtDNA methylation, and the appearance of mutations (insertions, deletions, and substitutions), are associated with the development of atherosclerosis. Damaged mtDNA was detected before the appearance of other atherosclerotic signs, suggesting that mtDNA damage may be the primary event that induces excessive ROS generation, disrupts mitochondrial membrane potential, and causes mitochondrial dysfunction, followed by the release of cytochrome C and the activation of apoptotic pathways. Furthermore, damaged mtDNA can be identified by the body as an endogenous DAMP, which activates the inflammatory response and contributes to the development of atherosclerosis [65].

Mitochondrial dysfunction was observed in VSMC isolated from human atherosclerotic plaques. These cells exhibited the presence of mtDNA mutations, reduced mitochondrial mass, and defects in ATP synthase. Impaired mitochondrial dynamics in SMC from atherosclerotic plaques can contribute to their proliferation. The morphology of the mitochondria is determined by fusion and fission processes, which also control the effectiveness of ATP synthesis, oxygen consumption, and the potential of the mitochondrial membrane. These processes are regulated by mitochondria-associated small GTPases, including the mitochondrial fusion protein mitofusin 2 (Mfn2), which reduces proliferation and promotes apoptosis of SMCs. Mitochondrial malfunctioning could exacerbate the activation of Poly (ADP-ribose) polymerase-1 (PARP-1), a critical component in the pathogenesis of atherosclerosis. Mitochondrial oxidative stress associated with atherosclerosis contributes to inflammation activation through the NF-kB-mediated pathway in macrophages. This process is characterized by a system of pro-inflammatory cytokines, adhesion molecules, and growth factors that, in turn, can trigger inflammatory signaling [66].

Chronic metabolic-inflammatory disorders can significantly impact the structure and function of the mitochondria. Addressing these conditions, such as obesity, hypertension, glucose intolerance, and hyperlipidemia, can facilitate mitochondrial regeneration. There is a reciprocal relationship between mitochondria and metabolic-inflammatory disorders, as both can exacerbate each other. This is illustrated in Figure 4. As a result, the term secondary mitochondrial dysfunction is employed, as it typically develops during a person's lifetime and is commonly associated with chronic diseases and age-related changes.

Achieving healthy mitochondrial function can be accomplished through various lifestyle adjustments, including adopting a balanced diet, engaging in regular physical activity, and taking supplements that contain essential vitamins (such as vitamins C, E, and biotin), minerals (zinc), or nutraceuticals (ubiquinone or CoQ10, NMN-precursor of NAD+, Quercetin, Astaxanthin, Resveratrol) [67].

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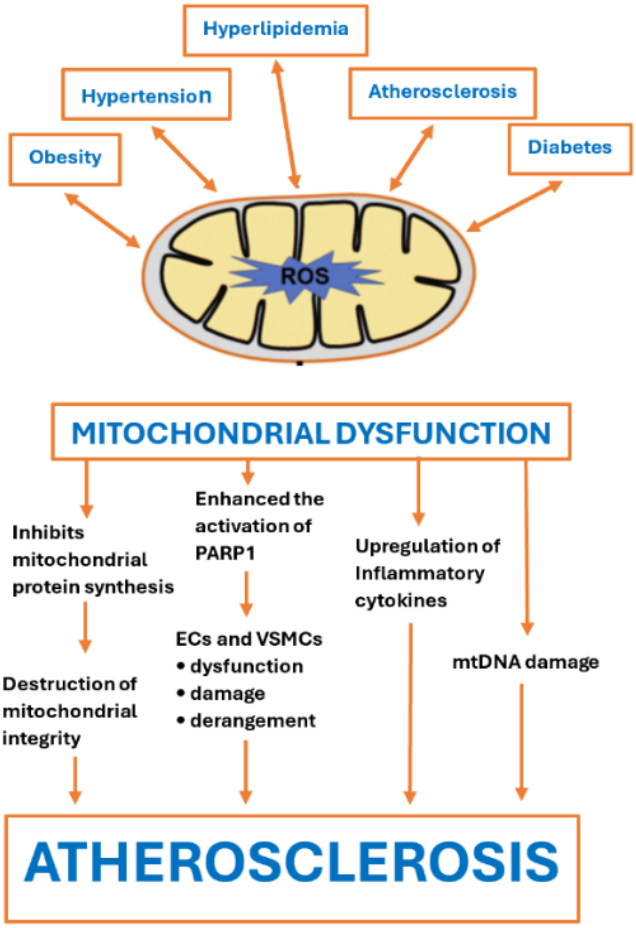

Figure 4: Bidirectional: metabolic- chronic inflammatory diseases cause mitochondrial dysfunction and vice-versa. Mechanisms of mitochondrial dysfunction induce atherosclerosis

Mitochondrial nutrients, which are necessary to maintain optimal mitochondrial function, have gained momentum in recent years. Studies have shown that a Mediterranean diet, characterized by the consumption of PBDs such as vegetables, fruits, and nuts, which are rich in polyphenols (isoflavones, phytoestrogens) and other phytochemicals (phytosterols, carotenoids, luteolin, organosulfur, terpenes, saponins) as well as polyunsaturated fatty acids from flaxseeds and sunflower seeds, can enhance mitochondrial function [68]. Polyphenols have been demonstrated to inhibit the activity of PARP-1, a critical component in the pathogenesis of atherosclerosis [69]. Enhancing mitochondrial function can accelerate the reversal of atherosclerosis, as depicted in Figure 4.

Potential benefits of Telomere manipulation in atherosclerosis

Aging is a progressive deterioration of biological functions that results in cellular malfunction and can lead to diseases such as hypertension, hyperlipidemia, NIDDM, CAD, and stroke. Numerous physiological changes occur as time passes, including genomic instability, epigenetic irregularities, loss of proteostasis, altered intercellular communication, abnormal nutrient absorption, altered mitochondrial function, depletion of stem cells, cellular senescence, and shortened telomeres. Telomeres are the protective caps at the ends of chromosomes, consisting of non-coding DNA sequences that prevent chromosomal breaks and clustering. With each cell division, telomeres become shorter, resulting in faster aging. Telomerase, a ribonucleoprotein enzyme, can synthesize telomeric repeats at the ends of chromosomes, slowing down the shortening of telomeres. By increasing telomerase enzyme activity, the rate of telomere shortening (TeS) can be slowed [70].

Various external factors, including lifestyle, nutrition, genetics, and heredity, can influence aging. Research on twin subjects has revealed that only 20-30% of an individual's lifespan is determined by genetic factors, while a significant portion depends on behavior and environmental factors. Some age-related diseases, such as hypertension, obesity, hyperlipidemia, NIDDM, and atherosclerosis, are associated with increased inflammation, oxidative stress, decreased telomerase activity, and TeS. Certain lifestyle habits, such as leading a sedentary lifestyle, smoking, experiencing emotional stress, being exposed to pollution, and engaging in unhealthy eating behaviors, can significantly increase oxidative stress and TeS, accelerating the aging and disease process [71].

Several longitudinal studies have demonstrated that TeS is strongly associated with mortality and age-related diseases such as acute myocardial infarction (AMI), atherosclerosis, stroke, hypertension, and NIDDM. In one population-based study, individuals with the longest telomeres had the lowest risk of dying during a 10-year follow-up period. In another study, participants with TeS had the lowest survival rates. Large-scale studies have also found that subjects with the shortest telomeres had a 17-66% increase in mortality risk compared to those with the longest telomeres. Thus, TeS are associated with early death, most likely due to cardiovascular risk factors, including AMI, CAD, NIDDM, hyperlipidemia, hypertension, and obesity. Consequently, individuals with the longest telomeres had the lowest risk of developing CAD, AMI, stroke, and vascular death [72].

Oxidative stress and persistent inflammation can lead to TeS, dysregulation of genes associated with telomeres, and a decrease in telomerase activity. The relationship between inflammation and TeS is reciprocal. Inflammatory stimuli can accelerate telomere attrition and result in telomere dysfunction and shortening. Conversely, TeS can contribute to low-grade inflammation [73].

Eating edible plants can be advantageous because they are abundant in compounds with antioxidant and anti-inflammatory properties. These compounds can counteract the negative impact of oxidative stress and persistent inflammation, contributing to the TeS. According to observational studies, consuming polyphenol/ phytochemicals-rich diets, such

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as vegetables, fruits, nuts, seeds, and their derivatives, can prevent TeS. This, in turn, can result in improved overall health and longevity. [74].

Elizabeth Blackburn, who was awarded the Nobel Prize, discovered that adopting a vegan diet can activate over 500 genes within a three-month period. This type of diet has the ability to activate genes that help prevent diseases and deactivate genes that cause chronic inflammatory diseases. Several methods for preserving telomeres include regular exercise, abstaining from smoking, and consuming a diet rich in plant-based foods. Dean Ornish and Elizabeth Blackburn conducted a study demonstrating how a PBD can increase telomerase activity, the enzyme responsible for maintaining the length of telomeres. The ability to preserve telomere length is crucial for longevity. Although it is impossible to reverse the numerical age, we can reverse the biological age, which can help mitigate the effects of chronic illnesses in our patients. Moreover, reversing patients' biological age by one or two decades will automatically decrease their risk of developing chronic inflammatory diseases, including atherosclerosis [75].

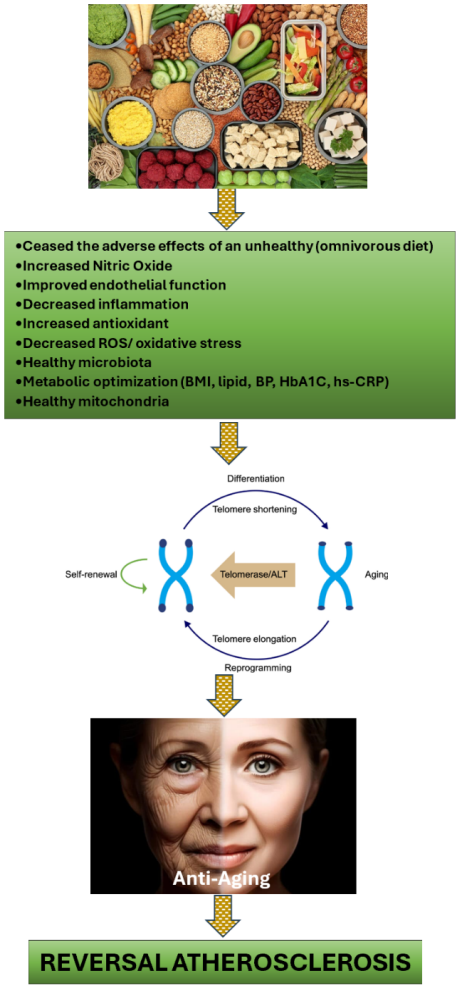

Figure 5: The process of preserving telomere length can inhibit the progression or even reverse atherosclerosis

Figure 5 exhibits the benefits of maintaining a healthy lifestyle, particularly by adopting a balanced PBD, in preventing TeS. By doing so, the aging process is slowed down or halted, thus minimizing the progression of atherosclerosis or potentially even regressing the condition.

Although we do not currently have the ability to modify our patients' genetics through the manipulation of mitochondria and telomeres, there is the potential to modify epigenetic markers to activate healthy genes and deactivate unhealthy ones. Epigenetics can influence the body's interpretation of specific DNA sequences, and as research progresses, the possibility of manipulating mitochondria and telomeres and even altering genes may become a reality in the future.

Conclusions

The importance of nutrition and health should be recognized. Studies have revealed that an unhealthy diet can lead to an increased likelihood of developing metabolic chronic inflammatory diseases, such as hypertension, hyperlipidemia, obesity, NIDDM, and atherosclerosis. To maintain optimal health and prevent these conditions, it is recommended to adopt a healthy lifestyle that includes balanced and proper nutrition, regular physical activity, abstaining from harmful substances (such as smoking, alcohol, and unhealthy foods), effective stress management, adequate sleep, and social support [76].

Managing atherosclerosis solely by concentrating on the local coronary vessel is no longer justifiable in today's medical practice. Trials from Courage (2007) to Ischemia (2019) have demonstrated that OMTs are as effective as performing PCIs in CCS patients [22-24,77]. Thus, the prerequisites for conducting PCIs have become progressively more stringent [8]. Therefore, combined OMTs and lifestyle modifications are the most reasonable choices for CCS patients. Given that most interventional cardiologists have traditionally concentrated on the local concerns of their patient's coronary arteries rather than addressing the metabolic-chronic inflammation issues. The ACC/AHA guidelines recommend that patients with CAD should primarily consume PBDs (COR 1 and LOE B-R), but it is essential to note that the majority of patients who have received PCIs have not adhered to this recommendation. Therefore, relying solely on PCIs to manage CCS patients offers only temporary respite. Ultimately, patients may experience recurrent atherosclerosis or encounter adverse consequences from the intervention, such as ISR or ST. Moreover, numerous interventional cardiologists do not adhere to this nutrient recommendation themselves, which makes it challenging for them to convey its efficacy with conviction, as they may not fully believe in its benefits or be hesitant to follow it due to the perception that it is unattainable. Although medications are critical to addressing systemic issues, neglecting a patient's dietary habits cannot be considered ethical or appropriate since numerous studies have shown that unhealthy diets

significantly contribute to the development of atherosclerosis. For the past three decades, experts in lifestyle medicine have endeavored to convince more doctors to adopt a lifestyle-changing approach. Unfortunately, progress in this area has been slow, and a significant change is needed as soon as possible, given the current crisis in the health sector and the world at large.

Our objective is to foster a deeper comprehension of the benefits and effectiveness of PBDs in alleviating atherosclerosis. We hope this review will prompt more extensive research and motivate the medical community to embrace healthier lifestyles.

Author Contributions

Conceptualization, D.M.; Writing-original draft, D.M.; Writing-review and editing, D.M., A.M.H., I.N.E.L., M.K.S., and H.U. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest:

The authors declare no conflict of interest.

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