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Progress in Investigating the Relationship between Omega-3 Polyunsaturated Fatty Acids and Coronary Heart Disease (CHD)

Jing Wang[1, *]

[1]Department of nursing, Hubei University of Chinese Medicine, Wuhan, China
*Corresponding author: li999shi@hhu.edu.cn

Abstract:

Coronary heart disease (CHD) is a globally common cardiovascular disorder, characterized by atherosclerotic lesions in the coronary arteries, leading to narrowing or blockage of the vessels, which subsequently causes myocardial ischemia, hypoxia, and even necrosis. This condition significantly impacts the daily life of patients and represents a major contributor to both morbidity and mortality on a global scale. Omega-3 polyunsaturated fatty acids (ω-3 PUFA), Principally extracted from marine pisces and certain plants, have been increasingly shown in recent years to be closely associated with various pathophysiological mechanisms related to CHD, which holds significant value in the prevention and treatment of CHD. This review offers a comprehensive summary of the sources of ω-3 PUFA, explores the pathophysiological mechanisms of CHD, and offers an in-depth analysis of the multifaceted contribution of ω-3 PUFA in mitigating the susceptibility to CHD, particularly focusing on their effects on lipid metabolism, endothelial function, and inflammatory pathways, thereby contributing new research perspectives for the tactics for the risk mitigation and administration of CHD, including both preventive measures and therapeutic interventions.

Keywords: Coronary Heart Disease; Omega-3 Polyunsaturated Fatty Acids; Atherosclerosis; Endothelial Function; Inflammation.

1. Introduction

Coronary atherosclerotic disease (commonly designated as coronary heart disease, or CHD) represents a cardiovascular condition that is frequently diagnosed worldwide and is widely recognized for its significant impact on public health. It refers to the occurrence of atherosclerotic lesions in the coronary arteries, resulting in vascular lumen stenosis or obstruction, which subsequently leads to myocardial ischemia, hypoxia and even necrotic heart disease. As a chronic disease, CHD seriously affects the daily life of patients. In 2021, cardiovascular disease was identified as a principal driver of mortality in the United States, significantly contributing to the nation's overall death rate and posing a major public health challenge, with 931,578 individuals who died as a result of these conditions. Among them, 375,476 people died from CHD, accounting for 40.3% of cardiovascular disease deaths [1]. Although the prevalence and mortality of CHD are high, current studies have proven that people can mitigate the risk of the disease and, to some extent, decelerate its progression through changing their daily lifestyle. There are many common risk determinants for CHD, for instance staying up late, nicotine use, drinking, etc. Alongside its role in averting CHD by avoiding these elements contributing to the risk, dietary factors are also crucial for both preventing and managing CHD, significantly influencing the reduction of its incidence and the effectiveness of treatment strategies. Currently, Numerous research have confirmed that following a healthy dietary pattern has a positive impact on the prevention and therapeutic management of CHD. Among these, the ingestion and absorption of omega-3 polyunsaturated fatty acids (ω-3 PUFA) is considered highly significant in preventing CHD. ω-3 PUFA, including alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), is a paramount constituent of a well-rounded nutrition pattern. The human organism be deficient in the ability to produce ω-3 PUFA on its own and needs to obtain them through a proper dietary intake from external sources. EPA and DHA are generally extracted from marine fish sources with high fat content. Numerous evidence from studies points to the advantages correlated with a higher intake of fish could help diminish the likelihood of myocardial infarction, hypertension, atherosclerosis and stroke [2]. Additionally, a variety of nutritional supplements, as exemplified by fish oil, cod liver oil, krill oil, and algae oil also contain EPA

and DHA [3]. ALA is mainly identified in vegetable oils, for instance flaxseed oil, perilla oil, walnut oil and hemp seed oil. A substantial body of research has confirmed the crucial protective role of ω-3 PUFA in cardiovascular health. However, there are still some uncertainties and controversies regarding the distinct mechanisms of ω-3 PUFA. Therefore, systematically sorting out and summarizing the research results concerning the influence of ω-3 PUFA in CHD not only has important academic value, but also has practical significance for guiding clinical practice and formulating public health policies. This article primarily examines recent advancements in research on the correlation between ω-3 PUFA and CHD.

2. ω-3 PUFA

2.1 Free Fatty Acids(FFA)

Free fatty acids (FFA) are divided into saturated fatty acids (SFA) and unsaturated fatty acids (UFA). Determined by the count of double bonds, UFA is divided into monounsaturated fatty acids (MUFA) and polyunsaturated fatty acid (PUFA).

2.2 Polyunsaturated Fatty Acids(PUFA)

Polyunsaturated fatty acids(PUFA)features two or more double bonds and is further divided into two different types according to the location of the double bonds, namely Omega-3 Polyunsaturated Fatty Acids (ω-3 PUFA) and Omega-6 Polyunsaturated Fatty Acids (ω- 6 PUFA).

2.3 Structure and nomenclature of ω-3 PUFA

ω-3 PUFA is a category of fatty acid with multiple double bonds in its molecular structure, usually containing 18 to 22 carbon atoms. Omega (ω): marks the final letter of the Greek alphabet. In chemical nomenclature, «omega» refers to the terminal carbon atom at the termination of a fatty acid›s carbon chain. «3» means that there is a double bond on the third carbon atom counting from the methyl end (that is, the terminal carbon atom) of the fatty acid. This is where the name «omega-3» comes from. ω-3 PUFA, encompassing ALA, EPA and DHA, are essential elements in maintaining a balanced and nutritious human diet.

3. Pathophysiological Mechanisms of CHD

3.1 Atherosclerosis

Atherosclerosis is the primary factor contributing to CHD, and high blood lipids will promote the development of atherosclerosis. Due to abnormal elevation of low-density lipoprotein cholesterol (LDL-C), LDL-C accumulates in the inner layer of the coronary artery wall, forming atherosclerotic plaques. Over time, these plaques will enlarge, causing arterial narrowing, reducing the circulation of blood to the cardiac muscle, as well as facilitating the advancement of atherosclerosis. It is now recognized that small, dense low-density lipoprotein (LDL) particles have a stronger atherogenic effect [4]. High-density lipoprotein (HDL) is pivotal in the reverse cholesterol transport (RCT) process, retrieving cholesterol from peripheral tissues, such as macrophages in artery walls, and subsequently carries it to the liver, where it undergoes metabolism and is eventually excreted. This helps reduce the buildup of cholesterol within artery walls. Additionally, HDL has antioxidant properties that prevent the oxidation of LDL, thereby reducing the risk of atherosclerosis. Therefore, balancing high HDL levels and low LDL levels is crucial to prevent atherosclerosis and CHD. At the same time, when serum triglyceride (TG) cannot be effectively controlled, cardiovascular events will occur more frequently [5]. Hyperlipidemia is usually accompanied by a decrease in HDL levels, which weakens the protective benefits of HDL on reverse cholesterol transport, alongside its antioxidant and anti-inflammatory functions, further exacerbating the risk of atherosclerosis. When an atherosclerotic plaque ruptures, the subendothelial material exposed to the bloodstream activates the coagulation system, leading to platelet aggregation and activation of coagulation factors, resulting in thrombus formation.

3.2 Endothelial Dysfunction

Endothelial cells are the lining of the endothelial lining of blood vessel. As a protective layer of the inner wall of blood vessels, they are crucial in controlling the tension of blood vessels, controlling blood flow and preventing thrombosis. Healthy endothelial cells can also promote vasodilation by releasing substances such as nitric oxide (NO). However, if the endothelial cells are damaged, their protective function is diminished, which will cause platelets to aggregate at the site of damage and form thrombus. Endothelial cell dysfunction can also lead to reduce NO production or decreased biological activity, impairing endothelium-dependent vasodilation, which can cause atherosclerosis, and leading to CHD [6]. When inflammation triggers the activation of endothelial cells, the adhesion molecules they express, for instance vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), promote the infiltration of leukocytes into the subendothelial space. This is one of the key pathophysiological processes of atherosclerosis [7,8]. Additionally, oxidative stress causes damage and dysfunction of endothelial cells through the excessive production of free radicals, as exemplified by reactive oxygen species (ROS) and reactive nitrogen species (RNS), giving rise to

thrombosis and contributing to the development of CHD [9]. Furthermore, various risk factors, encompassing hypertension, hyperglycemia, smoking, and hyperlipidemia have the potential to injure endothelial cells and destroy their barrier mechanism. Moreover, damage to endothelial cells by Oxidative stress constitutes one example of the critical and dominant mechanisms contributing to the development of CHD.

3.3 Inflammation

The inflammatory response within the coronary arteries is central to both the development and expression of CHD. It significantly drives the progression of the disease, influencing its clinical manifestations and overall impact. The process of atherosclerotic plaque formation begins when inflammatory cells, among them, monocytes and macrophages, infiltrate the artery wall, causing plaque formation and instability. These cells accumulate within the vessel wall and release a varied assortment of mediators, consisting of matrix metalloproteinases (MMPs), when stimulated by inflammatory cytokines, including TNF and IL-1β. These enzymes can degrade the matrix of the plaque fibrous cap. As lipids and necrotic material accumulate in the core of the plaque, the fibrous cap gradually thins, increasing the risk of plaque rupture. Once the plaque ruptures, the exposed material can induce platelet aggregation and thrombosis [10]. This ultimately leads to acute coronary syndrome (ACS), an acute manifestation of CHD that is a common and serious cardiovascular event. In this process, the inflammatory cytokines IL-1β, IL-6 and TNF, besides serum high-sensitivity C-reactive protein (hs-CRP) play key roles. IL-1β, IL-6 and TNF give rise to the activation of adhesion molecules in endothelial cells, promote the activation and migration of macrophages and T cells, and facilitate the growth and instability of atherosclerotic plaques. In addition, hs-CRP not only serves as a marker of inflammation, but also aggravates local and systemic inflammatory responses by activating endothelial cells, further promoting macrophages to secrete MMPs, and enhancing platelet reactivity [11]. These mechanisms interact to accelerate the pathological process of CHD and Increase the risk of plaque rupture, which can lead to the formation of blood clots. This heightened risk subsequently contributes to complications such as heart attacks and strokes.

4. Effect of 3 ω-3 PUFA on Coronary Heart Disease(CHD)

According to a particular study, Among the individuals with CHD (n=166) had significantly lower ω-3 PUFA levels than those without CHD (n=156). This result supports the idea that higher ω-3 PUFA levels may potentially possess the effect of inhibiting the occurrence of CHD, thereby reducing the risk of CHD [12]. When ω-3 PUFA <-4%, the ω-3 PUFA index is considered an indicator of increased risk of CHD, which also happens to reflect the average serum ω-3PUFA level in the United States [13,14]. Conversely when an individual's ω-3PUFA index is >8%, he is at low risk; research indicates that maintaining an ω-3 index above 8% is linked to a decrease in susceptibility to fatal CHD by approximately 35% [14-17].

4.1 Effects of ω-3 PUFA on Blood Lipids

Research evidence points to the fact that TG in patients with hyperlipidemia who took ω-3 PUFA preparations was 20% to 30% lower than other types of lipids [18]. n-3 PUFA treatment based on statin therapy can effectively reduce very low-density lipoprotein (VLDL) particles and TG levels [19]. The REDUCE-IT study was a multicenter, randomized, double-blind, prospective controlled trial that comprised 8,179 individuals receiving statin therapy, of whom 71% were CHD patients and 29% of the participants had diabetes and exhibited possessing a single risk element associated with cardiovascular disease. The experimental group received a high-dose purified EPA formulation (Vascepa 4 g/d, containing 3600 mg of EPA), while the control group received an equivalent amount of mineral oil. With an average observational period of around 4.9 years, during which participants were regularly monitored and assessed, the outcomes demonstrated that the experimental group experienced a notable decrease in TG levels relative to the control group (21.6% vs. 6.5%, $P<0.001$) [20]. The main mechanism by which ω-3 PUFA reduces TG is to downregulate sterol regulatory element-binding protein-1c (SREBP-1c), resulting in a decrease of liver fat synthesis; activating PPARα to strengthen fatty acid β-oxidation; and increasing the activity of lipoprotein lipase in peripheral capillary endothelial cells to promote fat breakdown [21]. ω-3 PUFA can also alter the size of lipoprotein particles. Findings from studies indicate that daily supplementation with ω-3 PUFA formulations has the potential to significantly lower small, dense LDL levels without changing HDL levels [22,23]. Overall, ω-3 PUFAs improve hyperlipidemia by lowering serum TG levels and altering lipoprotein particle size. Other research has shown that flaxseed oil or polyunsaturated fatty acids can inhibit thrombosis. For example, a study involving dairy cows investigated the effectuation of various fatty acids compositions with respect to cardiovascular disease prevention and found that supplementation with flaxseed oil or fish oil significantly reduced the atherosclerosis and thrombosis indices in 8 dairy cows [24]. This indicates that ω-3 PUFAs in flaxseed oil, alternatively fish oil exhibits a significant capacity to suppress

the advancement of atherosclerosis while also mitigating the risk of thrombosis.

4.2 Effects of ω-3 PUFA on endothelial function

ω-3 PUFAs have a positive effect on maintaining and improving endothelial function, including the production of NO and the reduction of pro-inflammatory mediators. ω-3 PUFAs can enhance vascular relaxation by increasing the bioavailability of NO. One study demonstrated that within bovine aortic endothelial cells, along with eNOS knockout mice, EPA promotes the biosynthesis of NO by activating eNOS through the stimulation of AMP-activated protein kinase (AMPK), which acts as a vital component in this process [25]. Another mechanism through which ω-3 PUFAs enhance NO production involves through direct stimulation of eNOS gene and protein expression. Alongside their role in enhancing NO production, ω-3 PUFAs also contribute to a reduction in oxidative stress, thereby further supporting cardiovascular health. Examinations carried out in cell cultures or with animal systems of vascular beds show that administering relatively substantial quantities of ω-3 PUFAs substantially enhances endothelial function by reducing ROS production, which is due to their direct modulation of sources of ROS production, such as the enzymes NADPH oxidase and iNOS, thereby ultimately leading to decreased peroxynitrite formation [26,27]. ω-3 PUFAs also regulate endothelial function through their anti-inflammatory effects. In particular, DHA has proven to be to reduce the expression of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) on endothelial cells and monocytes during culture [7,8]. Studies performed with rats indicate that EPA and DHA diminish the presentation of adhesion molecules on macrophages and lymphocytes [28,29]. Diminish presentation of adhesion molecules exerts functional impacts, culminating in diminished adhesion in the interaction between inflammatory cells and endothelial cells [29–31]. The previously mentioned suggests that ω-3 PUFAs attenuate the occurrence of endothelial dysfunction to some extent.

4.3 Increase ω-3 PUFA Levels to Exert Anti-inflammatory Effects

During the progression of atherosclerosis, ω-3 PUFAs can exert anti-inflammatory effects [32]. EPA and DHA can be converted into various lipid mediators that promote the resolution of inflammation, such as resolvin E (RvE) derived from EPA, with the involvement of lipoxygenase (LOX). RvE can reduce cellular damage at the inflammation site by inhibiting neutrophil migration and activation [33]. Research indicates that supplementation with ω-3 PUFAs exerts anti-inflammatory effects by restricting the synthesis of vital inflammatory cytokines IL-1β, IL-6, and TNF. EPA and DHA, in particular, can significantly lower the levels of these inflammatory cytokines, thereby reducing arterial inflammation. The MARINE and ANCHOR trials also found that EPA dose-dependently reduced levels of serum hs-CRP, oxidized LDL (ox-LDL), and lipoprotein-associated phospholipase A2 (Lp-PLA2), which are inflammation biomarkers associated with atherosclerosis [34]. This suggests that ω-3 PUFAs can, to some extent, alleviate the progression of atherosclerosis through their anti-inflammatory properties.

5. Conclusion

In summary, ω-3 PUFA have shown considerably effects in safeguarding against and treatment of CHD. Their mechanisms, including modulation of blood lipids, anti-thrombotic properties, augmentation of endothelial function, and inflammation-modulating actions, have been validated in numerous clinical and basic research studies. The combined effects of these functions contribute to reducing the formation and progression of atherosclerotic plaques and blood clots, thereby lowering the risk of CHD. However, current research has some limitations. There is relatively insufficient investigation into the long-term safety effects of ω-3 PUFAs, particularly at high doses. Further long-term follow-up research is required to assess potential adverse effects and long-term health impacts. Additionally, further investigation is required to determine the optimal dosage, administration methods, and interactions with other medications, in order to provide more comprehensive guidance for clinical use. Continued refinement and deepening of research on ω-3 PUFAs hold the potential for significant breakthroughs in the prevention and treatment of CHD.

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