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The Influence of Omega-3 Polyunsaturated Fatty Acids on Atherosclerotic Heart Disease

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Abstract. Cardiovascular diseases (CVD), dominated by atherosclerotic cardiovascular disease (ASCVD), are the leading cause of death among urban and rural residents in China. As of 2024, the China Report on Cardiovascular Health and Diseases 2024 shows that the incidence, total number of cases, and age-standardized incidence of cardiovascular diseases (CVD) in China have continued to show an upward trend. Among them, atherosclerotic cardiovascular disease (ASCVD) is a major contributor to the mortality burden of CVD. Although ASCVD is preventable and controllable, the report indicates that the control level of key risk factors for ASCVD (including smoking, obesity, hypertension, dyslipidemia, diabetes, etc.) still needs to be improved. Based on the antagonistic mechanism of omega-3 PUFA metabolites against atherosclerosis, this article reviews the structure and composition of omega-3 polyunsaturated fatty acids, their mechanisms of action, the influence of the mixture ratio of DHA and EPA on the changes of coronary atherosclerotic plaques, as well as their impact on people with atherosclerotic cardiovascular disease; and puts forward clinical medical recommendations based on the key risk factors of ASCVD. This article confirms that EPA and DHA play an important role in inhibiting inflammation by affecting the differentiation process of phagocytes, as well as the size and number of adipocytes. It is intended to remind clinicians that they should not only treat ASCVD, but also guide patients to prevent and manage ASCVD through dietary improvements in daily life, so as to reduce the prevalence and mortality of ASCVD.

Keywords: n-3 polyunsaturated fatty acids, Atherosclerotic cardiovascular disease, DHA, EPA, Disease prevention

1. Introduction

Atherosclerotic cardiovascular disease is a crucial cause of the death burden of CVD [1]. Omega-3 polyunsaturated fatty acids have significant protective effects against atherosclerosis, but the underlying mechanism remains unclear. The atherosclerosis antagonistic mechanism is based on the metabolic products of omega-3 polyunsaturated fatty acids [2]. It has been found that n-3 PUFA not only exerts its effects through the metabolic products of eicosanoids it generates, but also has a positive inhibitory effect on atherosclerosis through its own composition. This article analyzes the impact of omega-3 PUFA on atherosclerosis through the metabolic products that generate antagonistic mechanisms, and whether atherosclerotic diseases can be prevented through the

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interaction of omega-3 with other factors. Finally, through the analysis and discussion of clinical applications, the final results are widely promoted. The research in this article is beneficial for the public to prevent atherosclerosis.

2. The mechanism of action of omega-3 PUFA on atherosclerotic heart disease

2.1. The structure and composition of omega-3 fatty acids

Omega-3 polyunsaturated fatty acids (n-3 PUFAs) are a group of polyunsaturated fatty acids with the first double bond located at the third carbon atom from the methyl end. They are a type of polyunsaturated fatty acid that can play a positive anti-inflammatory role in cardiovascular diseases, mainly including docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and alpha-linolenic acid (ALA). Among them, dietary DHA and EPA can regulate atherosclerosis, and their mechanism of action may be related to inflammation.

2.2. The mechanism of action of DHA and EPA on atherosclerosis-related inflammatory responses

Atherosclerosis (AS), one of the common cardiovascular diseases, is a chronic inflammatory disease of the vascular intima caused by abnormal lipid metabolism. Inflammatory factors released by the body induce monocytes to enter the subendothelium, phagocytize oxidized low-density lipoprotein (LDL), and form foam cells. After the apoptosis of foam cells, a lipid core is formed. Smooth muscle cells migrate and proliferate to form a fibrous cap, which covers the lipid core and generates plaques. Atherosclerosis mainly occurs in large and medium-sized arteries [3].

DHA and EPA mainly exist in fish and certain seaweeds. Some studies have evaluated heart function by feeding mice a high-fat diet or a high-fat diet supplemented with DHA and EPA, and measured the effects of DHA and EPA on atherosclerosis. The results ultimately showed that the lesion burden of atherosclerosis in mice fed DHA and EPA was reduced by four times compared to the control group [4]. In the occurrence and development of AS, DHA and EPA can play a role in suppressing inflammatory responses through multiple aspects, thereby intervening in the progression of AS.

2.2.1. Regulation of the differentiation process of macrophages

Macrophages are the core cells in the regulation of adipose tissue and systemic inflammation, acting as both initiators and regulators of inflammation. A study first explored the changes in THP-1 cells (human acute monocytic leukemia cells, a typical model for studying macrophage differentiation) by detecting forward and side scatter (Figure 1B), and then presented the fatty acid profiles of macrophages derived from THP-1 after treatment with EPA and DHA (Figure 1). It was found that the incorporation of the corresponding fatty acids in the cells increased in a dose-dependent manner. Additionally, both EPA and DHA treatments reduced the level of arachidonic acid (AA) in immature macrophages, and the proportion of the anti-inflammatory fatty acid docosapentaenoic acid (DPA) also increased in macrophages treated with EPA [5]. By observing the changes in the scattered light characteristics of THP-1 cells treated with PUFA and the alterations in the expression of macrophage differentiation markers, it was demonstrated that PUFA can regulate the differentiation process of macrophages. Meanwhile, both EPA and DHA can reduce the pro-inflammatory AA level and

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increase the anti-inflammatory DPA level, thereby inhibiting the occurrence of intracellular inflammation.

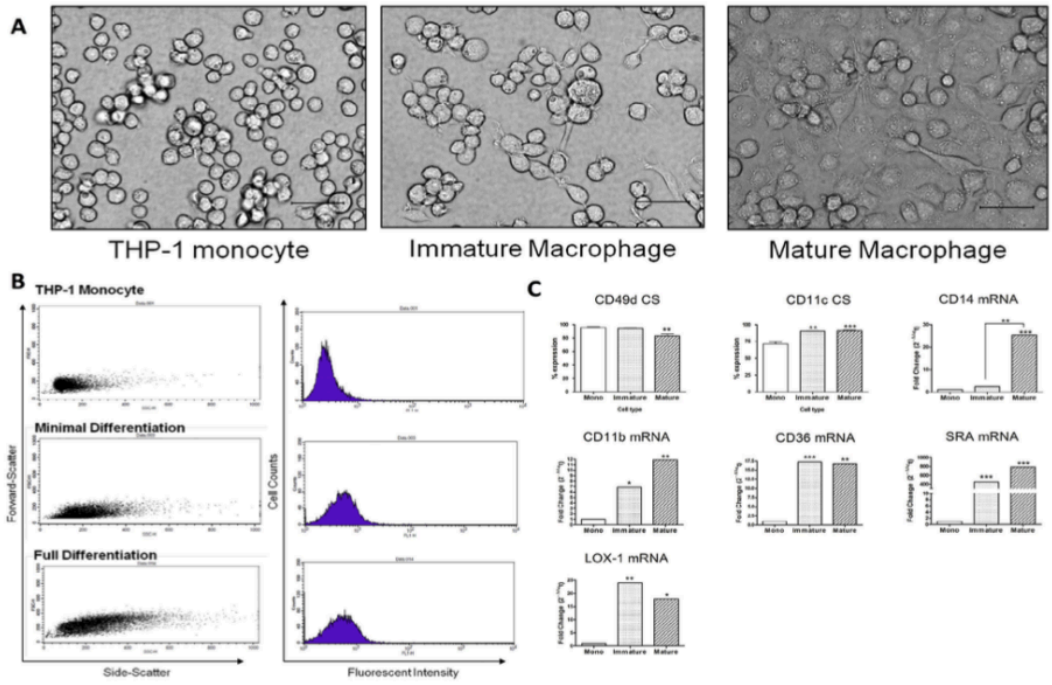


Figure 1. THP-1 immature and mature macrophage cell models Cellular morphology of THP-1 immature and mature macrophages. (A) Forward scatter/side scatter and autofluorescence; (B) each cell model. Expression of the cell surface (CS) differentiation markers CD49d and CD11c, and mRNA expression of the differentiation markers CD14 and CD11b, as well as the scavenger receptors CD36, SRA and LOX-1; (C) N > 3 'p < 0.05, "p < 0.01, ""p < 0.001 [5]

2.2.2. Regulating the size and number of fat cells

The size and number of adipocytes have a significant positive correlation with inflammation. Some studies have observed the electron microscopic images and changes in adipocyte size of obese-type gene (FA) and lean-type gene (Ln) mice under different dietary structures to reflect the functional status of DHA and EPA (Figure 2) [6]. The experiment showed that after dietary intervention, 25% of the fat cells in the fa BASE group were in the smallest size range (less than 500 square micrometers), while the fa EPA and fa DHA groups were 17%, the ln LA and fa ALA groups were 10%, and the fa LA group was only 6%. When comparing the largest fat cells (greater than 3000 square micrometers), 20% of the fat cells in the fa LA group fell into this range, 12% in the fa ALA group, and 3% to 6% in the other groups (Figure 2C). The results indicated that the fat cells in the fa EPA and fa DHA groups had the largest proportion in the smallest size range and the smallest proportion in the largest size range compared to the other groups. This suggests that EPA and DHA nutritional intervention can inhibit the abnormal enlargement of fat cells and is an effective way to improve adipose tissue inflammation.

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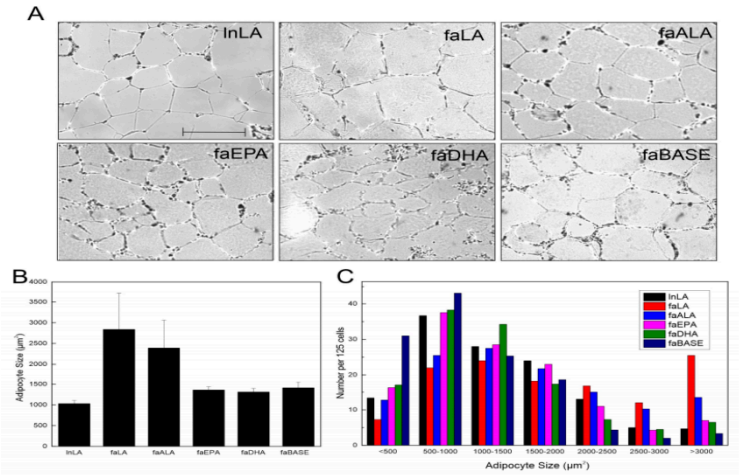


Figure 2. The effect of different polyunsaturated fatty acid diets on the size of adipocytes in mice: (A) Electron microscopic images of adipose tissue sections from each group of mice under different dietary structures; (B) 125 adipocytes were randomly selected from each mouse and the average adipocyte size was calculated. No significant correlations were detected by one-way ANOVA, and the data are presented as the mean ± SEM (n = 3-4). (C) Distribution of adipocyte sizes within a fixed range in different groups, with the data representing the number of cells within the fixed range for each group of mice (125 cells per group), and the differences among groups were determined by chi-square test [6]

3. The dosage ratio of DHA and EPA in the treatment of patients with coronary atherosclerosis

EPA can effectively reduce cardiovascular diseases, and imaging studies have shown that this is related to the quantifiable effect of EPA on coronary artery plaques. However, the mixture of EPA and DHA has not shown significant benefits in clinical practice. The experiment adopted the methods of systematic review and meta-analysis. By longitudinally measuring the standardized mean difference test data of the percentage change in plaque volume and lipid volume in patients in the statin + EPA group, the statin + EPA/DHA group, and the single statin group (as shown in Figures 3 & 4), it was indicated that the single agent of statin + EPA could more significantly reduce cardiovascular risks and affect the volume of coronary artery plaques [7].

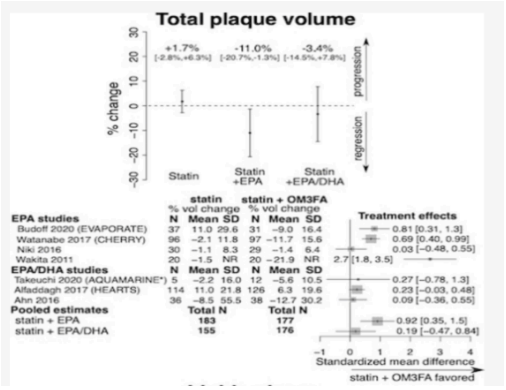


Figure 3. Total plaque volume

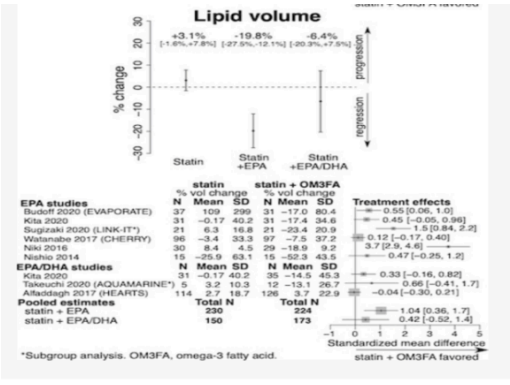


Figure 4. Lipid volume [7]

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4. Clinical applications

4.1. Treatment suggestion

In the lipid-lowering and anti-inflammatory treatment for patients with coronary atherosclerosis, it is recommended to prioritize the use of pure EPA preparations in combination with statins rather than EPA/DHA mixed preparations. Clinical data show that statins + EPA can reduce the total coronary plaque volume by 11.0% and the lipid volume by 19.8%, while the mixed preparations only reduce them by 3.4% and 6.4%, respectively [7]. At the same time, medical staff should pay more attention to the dietary structure of patients in their daily lives. According to the specific conditions of the patients' diseases and their living habits, such as smoking, obesity, hypertension, dyslipidemia, and diabetes, they should recommend that patients consume more foods rich in omega-3 unsaturated fatty acids, such as deep-sea fish, to reduce the risk of cardiovascular diseases and decrease the volume of coronary artery plaques.

4.2. Future treatment strategies

Colleges or research institutes can carry out clinical studies on different doses of high-purity EPA, combined with different EPA and DHA mixing ratios, to determine the optimal dosage. They can also explore the antagonistic mechanism of DHA on EPA and develop new n-3 PUFA compound preparations with synergistic effects based on clinical trial data, in order to minimize the cardiovascular risk of patients and reduce the volume of coronary plaques to the greatest extent.

At the same time, major hospitals can formulate individualized n-3 PUFA intervention plans for patients based on their genotypes, macrophage differentiation status, and fatty acid metabolism characteristics, and collect various data after treatment. According to the recovery of patients, the best n-3 PUFA intervention plan can be widely promoted. At the same time, patients' daily diet structure can be artificially controlled or combined with supplements for treatment, such as using n-3 PUFA in combination with folic acid and VB6 to improve atherosclerosis [8]. Post-treatment recovery data of the patients will be collected to provide data support for the combined intervention of functional foods and drugs.

5. Conclusion

Reports show that 76% of the global population lacks intake of omega-3 fatty acids [9]. This indicates that not only the Chinese population suffers from atherosclerosis due to an imbalance in fatty acid intake, but a large portion of the global population also experiences such cardiovascular diseases due to insufficient intake of omega-3 fatty acids. Among them, the inadequate intake of n-3 fatty acids from seafood is an important cause of these diseases [10]. This is because omega-3 mainly comes from deep-sea fish and nuts and seeds. The article discusses its main components, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), and based on the atherosclerosis antagonistic mechanism of omega-3 PUFA metabolites, it studies their regulation of macrophage differentiation processes. It also observes their effects on the size and number of fat cells and cell variations through electron microscope images of mouse cells. Through corresponding research results, it explores their mechanism of action and ultimately finds that both EPA and DHA can reduce pro-inflammatory AA levels and increase anti-inflammatory DPA levels, thereby inhibiting the occurrence of intracellular inflammation and intervening in the progression of AS.

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After confirming that EPA and DHA can inhibit inflammation, the article also analyzes the dosage ratio of DHA and EPA. A large amount of data indicates that compared with statin + EPA/DHA, statin + EPA alone can more significantly reduce cardiovascular risk and affect coronary plaque volume. In clinical applications, the treatment plan of EPA alone is more preferred. For future treatment strategies, it is recommended that major universities and research institutes strengthen the research on the "intrinsic effects of omega-3 fatty acids" as well as the "inhibitory effects of their combined use with other supplements on atherosclerosis". At the same time, it is suggested that patients, when following appropriate nutritional intervention treatment plans, also pay attention to reasonable exercise and diet combinations to maximize the treatment effect and reduce the harm caused by atherosclerosis.

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