ω-3 fatty acids in atherosclerotic cardiovascular disease (Review)

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Abstract. Atherosclerotic cardiovascular disease (ASCVD) is one of the most common chronic diseases in the world. Epidemiological evidence and clinical trials have shown that ω-3 fatty acids have a variety of promoting effects in reducing the risk of ASCVD, but different conclusions of large randomized controlled trials make their clinical use in the prevention and treatment of ASCVD controversial. The present review focuses on the pharmacological mechanism, clinical trials and evidence value of clinical applications of ω-3 fatty acids in order to provide theoretical and practical evidence for the clinical application strategy, and follow-up research and development of ω-3 fatty acids as anti-ASCVD drugs.

Contents

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Abbreviations: ASCVD, atherosclerotic CV; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; TGRL, triglyceride-rich lipoproteins; PUFA, polyunsaturated fatty acid; ALA, α-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; PPAR, peroxisome proliferator-activated receptors; HTG, hypertriglyceridemia; HDL-C, high-density lipoprotein cholesterol; SREBP-1, sterol regulatory element binding protein-L; RvE1, resolvin E1; NO, nitric oxide

Key words: ω-3 fatty acids, atherosclerotic cardiovascular disease, triglycerides, clinical application

1. Introduction

According to the World Health Organization, atherosclerotic cardiovascular (CV) disease (ASCVD) is one of the most common diseases in the world and also a notable cause of mortality, mostly occurring in low- and middle-income countries (1). Although statin therapy has been shown to reduce the risk of CV events by 25-45%, even when target low-density lipoprotein cholesterol (LDL-C) levels are met, a CV residual risk still exists (2). Genetic and epidemiological studies have shown that persistent CV residual risk may be associated with other forms of dyslipidemia, such as elevated levels of triglyceride (TG)-rich lipoproteins (TGRLs) (3,4). However, from a pharmacological aspect, the extent to which statins alone improve TG levels in patients with ASCVD is insufficient or even weak (5). At present, the therapeutic methods that may be used to reduce TG levels in the clinic mainly include niacin, fibrate and ω-3 fatty acid drugs (6). In recent years, ω-3 fatty acids have attracted increased attention in the prevention and treatment of ASCVD by lowering TG levels. In a large randomized CV outcome trial, the CV residual risk reduction effect of ω-3 fatty acids on patients with well-controlled LDL-C levels and elevated TG levels was studied, but the results did not show a consistent ASCVD risk reduction effect (7,8).

ω-3 polyunsaturated fatty acids (PUFAs) are part of the essential PUFAs of the body and have a number of effects apart from lowering TG levels. Among others, these fatty acids also have anti-inflammatory, anti-thrombotic, anti-oxidation and anti-arrhythmia effects, as well as being able to improve endothelial function and insulin resistance (9). ω-3 is the technical term used to describe the structure of a particular PUFA family, indicating the first double bond position of the fatty acid from the methyl end, between the third and fourth carbon (10). The main ω-3 fatty acids include α-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The only way to obtain it is from dietary sources (11). The simplest ω-3 fatty acid is ALA, which exists in plants. After ingestion, the human body mainly metabolizes EPA in the liver and then further metabolizes DHA through various enzyme actions and β-oxidation (12). In the human body, the metabolism is affected by various factors, such as age, sex, hormonal changes and genetics, and the conversion rate of ALA to EPA and DHA is usually limited, resulting in certain health benefits of ALA (12). In healthy young men, only ~8% of ALA is converted to EPA and <4% is converted to DHA. In healthy women, the conversion rate of ALA is

higher than that in adult men due to increased estrogen levels before menopause, and ~21% of ALA is converted to EPA and ~9% is converted to DHA (13,14). Both EPA and DHA may be beneficial for ASCVD treatment, but their mechanisms of action have not been fully elucidated. Existing studies have shown that DHA has a key role in the central nervous system and retina, and is also an essential fatty acid for fetal development (15). Unlike DHA, EPA is mainly concentrated in artery walls and atherosclerotic plaques, promoting the release of anti-inflammatory mediators (16). However, the benefits of a combination of EPA and DHA ω-3 fatty acids in the treatment of ASCVD are inconsistent with those of either EPA or DHA alone, possibly due to differences in the formulation, dosage or potential anti-regulatory effects of DHA. Therefore, in the present study, the application status of ω-3 fatty acid drugs was reviewed and the relevant knowledge of ω-3 fatty acid pharmacology, clinical trials and the main guidelines or consensus at home and in other countries for the treatment of ASCVD were summarized in order to provide references for the rational clinical application of ω-3 fatty acid drugs.

2. Clinical pharmacological effects of ω-3 fatty acids

Reducing TG levels. TGs are not directly involved in the process of atherosclerosis, but TGRLs, such as very LDL (VLDL), chylomicron and residual particles are causally related to the occurrence of ASCVD independently of LDL (17). TGRLs are aggregated by macrophages in the subendothelial layer and form foam cells, promoting the formation of fat streaks, which are early atherosclerotic plaque lesions. With the accumulation of plaque, when the plaque surface is eroded or ruptured, thrombosis is easily formed, and ASCVD and other CV events are triggered (18). EPA and DHA are potent fatty acid agonists of peroxisome proliferation-activated receptors (PPAR), which are part of the nuclear hormone receptor superfamily. Various genes involved in the regulation of lipid metabolism are formed by binding to PPAR reactivity regulatory elements to form active transcriptional complexes (19). PPAR-α, which is involved in fatty acid metabolism, is one of the isomers of PPAR. After activation, fatty acid β-oxidation in the liver increases, TG secretion decreases and lipase activity increases, accelerating VLDL clearance and increasing high-density lipoprotein cholesterol (HDL-C) (20). The synthesis pathways of various cholesterol and fatty acids, and the assembly of VLDL are regulated by sterol regulatory element binding protein-1 (SREBP-1) (21). In mouse models, ω-3 fatty acids reduce the expression of proteins involved in VLDL synthesis by activating PPAR-α and inhibiting SREBP-1, thereby reducing their release and lowering plasma TG levels (22). Therefore, ω-3 fatty acids reduce plasma TG levels by reducing VLDL production, increasing VLDL clearance, inhibiting lipogenesis, increasing β-oxidation and increasing lipase activity.

Anti-inflammatory. Atherosclerosis is essentially a chronic inflammatory disease, and reducing and eliminating inflammation is essential to restore homeostasis and combat chronic diseases (23). ω-3 fatty acids have a marked role in regulating lipid rafts and affecting cell membrane fluidity. They can integrate themselves into the phospholipid bilayer of the neutrophilic cell membrane and produce a series of hormone-like lipid mediators such as prostaglandins, which mainly exert anti-inflammatory effects on tissue injury and infection sites (24). ω-3 fatty acids can also regulate the production and secretion of cytokines and chemokines by changing gene regulation, weaken the M1 polarization of macrophages and promote M2 polarization, improve the function of macrophages and ultimately promote phagocytosis (24). ω-3 fatty acids promote the decomposition of lipids and reduction of inflammation by producing specialized lipid-promoting mediators, such as catabolism and protectors, and help restore homeostasis after tissue injury, thus reducing the formation of ASCVD (25). Resolvin E1 (RvE1) is a specialized pro-decomposition lipid mediator derived from EPA that has a key role in resolving inflammation and tissue homeostasis. T-helper type 17 (Th-17) cells have a tissue-destroying function in autoimmune and chronic inflammatory diseases by secreting interleukin (IL)-17. RvE1 has been shown to block T-cell activation, Th-17-cell stimulation and chemical attraction, thereby promoting the resolution of inflammation (26). Studies have found that if healthy participants receive >2 g ω-3 fatty acids per day, endotoxins stimulate monocytes, and tumour necrosis factor α, IL-1 and IL-6 are reduced, suggesting that ω-3 fatty acids may have an anti-inflammatory role by reducing the expression of pro-inflammatory cytokines and adhesion molecules at inflammatory sites (27). Other studies have reported anti-inflammatory mechanisms of ω-3 fatty acids, including the downregulation of nuclear factor κB (NF-κB) by ω-3 fatty acids after binding to g-protein-coupled receptor 120. NF-κB and activator protein 1 have an anti-inflammatory role (28-30). Through the polarization of $CD4^+$T lymphocytes towards Th-2 cells, ω-3 fatty acids maintain a balance of Th-1 and -2 cells, promote the regression of inflammation and thus inhibit the development of atherosclerosis (31).

Improvement of endothelial function. Endothelial cell dysfunction has a causal relationship with atherosclerosis and is directly related to an increased risk of ASCVD (32); therefore, improving endothelial cell function is a new approach to enhance the benefits of ASCVD treatment. Vascular endothelial cells can synthesize and secrete vasodilator factors such as nitric oxide (NO) and vasodilator factors such as angiotensin II and endothelin-1. When the secretion of these two factors is unbalanced or the availability of NO is reduced, endothelial dysfunction is caused (33). NO is an important vascular endothelial protective factor, which can not only relax blood vessels and relieve vasospasm, but also protect vascular endothelium through anti-oxidation, anti-inflammatory and anti-platelet aggregation (34). As a signaling molecule, NO produces cyclic guanosine monophosphate by activating soluble guanosine cyclase, which activates downstream signaling molecules, causing vasodilation and reducing inflammation (35). ω-3 fatty acids have been shown to improve endothelial function through multiple mechanisms. On the one hand, ω-3 fatty acids can enhance vasodilation by increasing the activity of endothelial NO synthase. On the other hand, ω-3 fatty acids can reduce the vasoconstriction effect of endothelin-1 and reduce oxidative stress to improve endothelial function (25). In human endothelial cells, ω-3 fatty acids can inhibit the expression of pro-atherosclerotic and -inflammatory proteins

induced by cytokines, thereby improving the vasomotor ability and arterial compliance of patients with ASCVD, and reducing the production of biomarkers of inflammation and oxidative stress (23).

3. ω-3 fatty acid clinical trials

For a long time, scientists have been committed to the study of the value of ω-3 fatty acids in the clinical prevention and treatment of ASCVD. As early as >30 years ago, Burr *et al* (36) found that deep-sea fatty fish or fish oil capsules were able to reduce the all-cause mortality of patients with myocardial infarction by ~29%. In the GISSI-P study conducted in Italy (37), 11,324 patients with myocardial infarction within 3 months were included and followed up for an average of 3.5 years. It was found that in the experimental group treated with 1.0 g/day ω-3 fatty acids (EPA/DHA, 1:2), the risk of primary endpoint events, death and CV-associated death was reduced by 15, 20 and 30%, respectively. In the JELIS study conducted in Japan (38), 18,645 patients aged 40-75 years with total cholesterol ≥6.5 mmol/l (251 mg/dl) were selected as study subjects and the experimental group was given 1.8 g/day EPA drug therapy, with an average follow-up of 4.6 years. The results showed that the EPA-treated group had a 19 and 28% lower risk of primary endpoint events and unstable angina, respectively, and no reduction in the risk of coronary artery death or myocardial infarction. Subsequently, between 2010 and 2013, several randomized controlled studies on ω-3 fatty acids published by Rauch *et al* (39), ORIGIN trial investigators *et al* (40) and the Risk and Prevention Study Collaborative Group *et al* (41) did not obtain the desired positive results. In a randomized, placebo-controlled trial conducted in 2018 in the UK (42), a total of 15,480 patients with diabetes aged ≥40 years and without ASCVD were included after being treated with 1.0 g/day ω-3 fatty acids (EPA+DHA) and followed for an average of 7.4 years. The results showed no marked reduction in the risk of serious vascular events. The following year, a randomized, placebo-controlled, 2x2 factorial design trial, VITALs, was conducted in the US, and a total of 25,871 patients aged ≥50 years without ASCVD and cancer were treated with 1.0 g/day ω-3 fatty acids (EPA+DHA) and followed up for an average of 5.3 years. The results showed that the risk of major adverse CV events was not markedly reduced (43). Inconsistent findings have led to controversy over the clinical value of ω-3 fatty acids in patients with ASCVD. More recently, with the publication of the important REDUCE-IT study (44), which showed improved CV benefits through the use of ω-3 fatty acids, the application of ω-3 fatty acids in ASCVD has once again attracted attention. REDUCE-IT was a multicenter randomized, double-blinded, placebo-controlled trial of 8,179 patients with CV disease or type 2 diabetes with CV risk factors. The fasting TG range after statin treatment was 1.5-5.6 mmol/l (135-500 mg/dl) and the LDL-C range was 1.1-2.6 mmol/l (41-100 mg/dl), treated with 4 g/d icosapent ethyl (IPE) or mineral oil, respectively, and the median follow-up was 4.9 years. The results showed that IPE markedly reduced the risk of primary endpoint events (such as CV death, non-fatal myocardial infarction, non-fatal stroke and coronary revascularization or unstable angina complex events) by 25% and also markedly reduced the risk of key secondary endpoint events, while no reduction in the risk of all-cause death was observed, and based on the REDUCE-IT study, IPE is the only ω-3 fatty acid approved by the Food and Drug Administration in the United States, Canada and the European Union for CV risk reduction indications in patients with CVD or diabetes with other ASCVD risk factors. The results of the STRENGTH (45) and OMEMI (46) studies published after the REDUCE-IT study did not achieve the expected significant effect in the CV effects of ω-3 fatty acids in patients with ASCVD. STRENGTH was a multicenter, double-blinded, placebo-controlled randomized clinical trial involving 13,078 at-risk patients with CV treated with statins with hypertriglyceridemia (HTG) and low HDL-C levels from 22 countries who were treated with 4 g/day ω-3 carboxylic acid or corn oil, respectively, with a median follow-up of 3.5 years. The results showed no benefit in the risk of major adverse CV events in the ω-3 carboxylic acid group. The OMEMI study was also a multicenter, randomized, double-blinded, placebo-controlled clinical trial involving 1,027 Norwegian patients aged 70-82 years with recent acute myocardial infarction who were treated with 1.8 g/day ω-3 fatty acids (EPA+DHA) and followed up for an average of 2 years. The results showed that ω-3 fatty acids did not reduce the risk of primary endpoint events.

4. Major national and international guidelines or consensus on the use of ω-3 fatty acids for the treatment of ASCVD

The 'Guidelines for the Management of Dyslipidemia' issued by the European Society of Cardiology and the European Atherosclerosis Society in 2019 proposed that patients with ASCVD and TG ranging from 1.5-5.6 mmol/l (135-500 mg/dl) after receiving statin therapy were at high or very high risk. The combination of ω-3 fatty acids (2 g IPE, twice daily) and statins should be considered for lipid-lowering therapy (47). The Guidelines for the Primary Prevention of CV Diseases in China released in 2020 suggest that individuals at high risk of ASCVD should be given a high dose of ω-3 fatty acids [IPE 2 g if the TG level is still >2.3 mmol/l (200 mg/dl) after receiving a moderate dose of statin therapy, 2 times daily] to further reduce the risk of ASCVD (48). The Chinese Expert Consensus on Secondary Prevention after Coronary Artery Bypass Transplantation published in 2020 proposed that for patients with ASCVD combined with HTG, supplementation with high-purity EPA ω-3 fatty acids may be considered for secondary prevention to further reduce CV events, while whether to supplement EPA+DHA mixed type was not mentioned (49). The Expert Consensus on the Comprehensive Management of Blood Pressure and Lipids in Chinese Hypertensive Patients released in 2021 pointed out that for patients with ASCVD, TG levels and the incidence of CV events may be reduced to a certain extent after treatment with a large dose of ω-3 fatty acids (IPE 2 g, twice a day) (50). The Expert Consensus on the Diagnosis and Treatment of Diabetes Combined with CV Diseases released in 2021 pointed out that patients with high or very high risk of CV disease, on the basis of receiving strict lifestyle intervention and statin therapy, if the TG level is still >2.3 mmol/l (200 mg/dl), the recommendation favors the use of high-dose ω-3 fatty acids (IPE 2 g, 2 times daily) to further reduce the risk of

CV disease (51). According to the 2021 'Stroke Prevention Guidelines for Stroke and Transient Ischemic Attack Patients' issued by the American Heart Association/American Stroke Association, for patients with ischemic stroke and transient ischemic attack, if the fasting TG range is 1.5-5.6 mmol/l (135-500 mg/dl) and the LDL-C range is 1.0-2.6 mmol/l (41-100 mg/dl), they had been using medium-high intensity statins and had glycosylated hemoglobin A1C levels of <10% without pancreatitis, atrial fibrillation and severe heart failure, a high dose of ω-3 fatty acid (IPE 2 g, twice daily) treatment was able to reduce the risk of stroke recurrence (52). The 2021 American College of Cardiology 'Management Consensus on Reducing the Risk of ASCVD in Patients with persistent HTG' points out that lifestyle interventions, TG lowering therapy with statins and prescription of pure fish oil preparations are needed to reduce the risk of ASCVD in patients with persistent HTG (53). The 2022 Diabetes Guidelines issued by the American Diabetes Association indicate that in patients with ASCVD or other CV risk factors who were treated with statins and had LDL-C under control but a TG range of 1.5-5.6 mmol/l (135-500 mg/dl), increased use of IPE may be considered to reduce CV risk (54). The Chinese expert consensus on the role of ω-3 fatty acids in the prevention and treatment of CV disease released in 2023 pointed out that patients with a high or very high risk of ASCVD, on the basis of strict lifestyle intervention and statin therapy, if the TG level is still >1.5 mmol/l (135 mg/dl), high doses of IPE (4 g/day) are recommended to further reduce CV risk (55). According to the Chinese Lipid Management Guidelines Issued by the Joint Expert Committee for the Revision of Chinese Lipid Management Guidelines in 2023, it is recommended to give a large dose of IPE (2 g, twice a day) to patients with ASCVD and high-risk groups if their TG level is still >2.3 mmol/l after receiving moderate-intensity statin therapy or high-purity ω-3 fatty acids, fibrates to further reduce the risk of ASCVD (56).

5. Summary and future perspectives

Although several large randomized controlled trials of ω-3 fatty acids for the prevention and treatment of ASCVD have reported mixed conclusions, in recent years, domestic and foreign expert consensus and guidelines still recommend the use of ω-3 fatty acids to prevent residual CV risk in patients with ASCVD who are unable to control high levels of TG after using statins and fibrates. The mechanism of action of ω-3 fatty acids is complex, and it is not yet clear which mechanism is responsible for reducing the risk of ASCVD. The effects of ω-3 fatty acids on lowering TG levels, their anti-inflammatory effects and ability to improve endothelial function may help explain their positive role in reducing the risk of ASCVD. With the continuous in-depth research on drug prevention and treatment of dyslipidemia and clinical management strategies, in addition to paying attention to the effect of conventional drug treatment, early risk warning and auxiliary management of ASCVD are also being carried out. Combined with current relevant research conclusions, ω-3 fatty acids show a high benefit-risk ratio in the prevention and treatment of ASCVD. It should be considered as an adjunct to lipid-lowering drug therapy such as statins. It is recommended that clinicians carefully consider this new treatment option, educate patients at risk of ASCVD regarding its important benefits and pay attention to the evaluation of patients with ASCVD in clinical care.

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Availability of data and materials

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Authors' contributions

XX and XL performed the literature search and co-wrote the manuscript. RL, LF and FH performed the literature search and reviewed the literature and the manuscript. XX provided guidance for the study and revised the manuscript. All of the authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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