Review

ICOSAPENT ETHYL AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE IN TYPE 2 DIABETES (NARRATIVE REVIEW)

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This narrative review was aimed to analyze the current views on the biochemical and molecular mechanisms of ω-3 polyunsaturated fatty acids (ω-3 PUFAs), in particular icosapent ethyl (IPE), in atherosclerotic cardiovascular disease (ASCVD) and type 2 diabetes mellitus (T2D). The results of experimental, cohort, prospective, randomized clinical trials confirm the prospects of using IPE to prevent and treat ASCVD in T2D.

Search Techniques. Databases from Scopus, Science Direct (from Elsevier), EBSCO, PubMed, and Medline were all searched. To find trials that were missed by the web search, a manual search of the publishing bibliographies was conducted.

Keywords: ω-3 polyunsaturated fatty acids, icosapent ethyl, atherosclerotic cardiovascular disease, type 2 diabetes mellitus.
1. Introduction

An atherosclerotic cardiovascular disease (ASCVD) is the main complication and cause of morbidity and mortality in type 2 diabetes (T2D) [1-3]. Diabetic dyslipoproteinemia remains a major risk factor for ASCVD in these patients. However, there is accumulating evidence that lipid-lowering treatment contributes to long-term glucose homeostasis alterations and T2D [4]. Due to increased triglyceride (TG) levels, despite reaching target levels of low-density lipoprotein cholesterol (LDL-C), patients nevertheless may have a risk of ASCVD [5,6]. Patients with persistently elevated fasting TG (>2.26 mmol/L) and maximally tolerated statin therapy may benefit from fibrates or ω-3 polyunsaturated fatty acids (ω-3 PUFAs) for additional LDL-C lowering.

The randomized clinical trial (RCT) PROMINENT (Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes) demonstrated no advantage of peremafibrate in reducing ASCVD risk in T2D patients with hypertriglyceridemia (HTG) and high-density lipoprotein cholesterol, with simultaneous increase of LDL-C level [7].

High-risk ASCVD patients with HTG should receive icosapent ethyl (IPE, a highly purified eicosapentaenoic acid [EPA]), according to international standards [8]. REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl Intervention Trial) found that HTG patients who took 2 g of IPE twice a day had a considerably decreased incidence of ischemic events, including cardiovascular (CV) mortality [9]. RESPECT-EPA (Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy-Statin and Eicosapentaenoic Acid Trial) met the secondary endpoint with a relative risk decrease attributable to IPE therapy [10].

The aim of this narrative review is to evaluate and summarize the research on the benefits of ω-3 PUFAs and particularly IPE in ASCVD and T2D, as well as any potential biochemical and molecular mechanisms behind these improvements.

2. Ω-3 PUFAs and diet

High consumption of ω-3 PUFAs is associated with decreased cardiometabolic risk and reduced inflammatory activity. At the same time, circulating EPA blood levels in Western countries’ residents are usually low [11,12]. It is generally assumed that increased intake of EPA and other ω-3 PUFAs with a healthy diet should reduce the risk of ASCVD [13]. However, the actual intake of ω-3 PUFAs is usually insufficient due to their limited availability [14]. The National Health and Nutrition Examination Survey reports that fasting glucose levels in obese adults are inversely proportional to EPA intake [15]. Nutritional models such as the Mediterranean Diet, Dietary Approaches to Stop Hypertension, and a controlled carbohydrate diet are known to be effective in reducing ASCVD risk factors [16]. According to the results of intervention studies, various dietary patterns may also be appropriate for people with impaired glucose tolerance (IGT), including Mediterranean and low-carbohydrate diets [3].

3. Icosapent ethyl

In the United States, three prescription forms of ω-3 PUFAs are approved for the treatment of adults with severe HTG: (1) a mixture of ω-3 PUFA ethyl ester, mainly EPA and docosahexaenoic acid (DHA); (2) IPE, ethyl ester of EPA; and (3) ω-3 carboxylic acids, a mixture of ω-3 PUFAs in the form of free fatty acids (FFA) [14]. In the approved doses, all drugs significantly reduce the levels of TG and very low-density lipoprotein cholesterol (VLDL-C). Formulations containing DHA can also increase LDL-C, which is not accompanied by an increase in non-HDL-cholesterol (non-HDL-C) levels [17]. IPE is approved as a dietary supplement to lower TG levels in adult patients with severe HTG (≥5.65 mmol/L) [14]. The American Heart Association amended its treatment guidelines for stable chronic coronary syndrome (CHD) with T2D. IPE was named a first-line medication for CHD and T2D patients with TG >1.69 mmol/L [8].

3.1 Mechanism of action

IPE is a unique drug because it contains exclusively EPA, which is believed to be able to reduce the risk of ASCVD. In contrast to ω-6 arachidonic acid (AA), which is converted to pro-inflammatory and prothrombotic forms of eicosanoids, ω-3 EPA has the opposite effects [16]. Increased EPA/AA ratio increases cardiovascular health benefits, while lower values are associated with an increased risk of ASCVD [18]. The products of ω-3 PUFAs metabolism, namely protectins, resolvins (Rvs), and maresins, have anti-inflammatory properties and counteract the activation of the inflammatory response in ASCVD [11]. Rvs bind to and activate G-protein-coupled receptor 32 (GPR32). Signaling through GPR32 actively inhibits inflammatory processes in atherosclerotic plaques [2,19,20]. Agonism of GPR120, an
3.3 Icosapent Ethyl and ASCVD

Several mechanisms for the protective role of EPA in ASCVD have been proposed: modulation of lipoprotein lipase activity; changes in lipid profile; lowering blood pressure (BP); reducing the tendency to thrombosis; anti-inflammatory effect; improvement of endothelial function; reduction of tumor necrosis factor-α (TNF-α) expression [12,27,28]. V. Musazadeh et al. [29] used a random effects model to study the effect of ω-3 PUFA on BP, and the sensitivity analysis was performed using the cross-validation method. A pooled assessment of 10 meta-analyses revealed a significant reduction in systolic BP (SBP) and diastolic BP (DBP). The obtained results indicate that ω-3 PUFAs can positively affect SBP and DBP parameters.

Ω-3 PUFAs can lower hypertension by controlling caveolae composition, activating NO synthase, enhancing endothelial function, and reducing systemic vascular resistance by increasing vasodilator mediator synthesis and inhibiting vasoconstrictor mediators. Antihypertensive ω-3 PUFAs activate thioredoxin reductase 1, heme oxygenase, and superoxide dismutase, protecting endothelial cells from oxidative stress (OS). The anti-inflammatory activity of ω-3 PUFAs may also contribute to its antihypertensive effects [11,30,29].

It should be noted that there are differences between DHA and EPA in terms of their effects on blood vessels and myocardium. EPA seems to be especially good at slowing down the progression of ASCVD because its molecular properties improve how redox processes work at the cell membrane level [27].

3.3 The effect of IPE on lipid metabolism

A meta-analysis of 45 RCTs that enrolled 2674 patients with T2D showed that daily intake of ω-3 PUFAs for 6 months was associated with a significant reduction in LDL-C, VLDL-C, TG, glycated hemoglobin A1c (HbA1c), and plasma TNF-α levels [31]. However, it has been demonstrated that using EPA and DHA in patients with T2D and ASCVD did not improve metabolic and inflammatory status [17]. According to the results of ORIGIN (The Outcome Reduction with an Initial Glargine Intervention Trial), there was no statistically significant effect of 0.9 g/day of ω-3 PUFA ethyl esters on reducing mortality due to ASCVD in patients with T2D [32]. In addition, the results of the ASCEND (A Study of Cardiovascular Events In Diabetes) trial demonstrated that in patients with T2D without ASCVD, there was no significant difference in the incidence of major adverse cardiovascular events (MACE) between patients receiving ω-3 PUFAs and the placebo group [33]. However, the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico (GISSI-Prevenzione Trial) showed that low-dose ω-3 PUFAs (1 g/day) reduced overall mortality and sudden death due to ASCVD [34]. According to the JELIS (Japan EPA Lipid Intervention Study), patients with hypercholesterolemia treated with statins and highly purified EPA (1.8 g/day) experienced a 19% relative reduction in the incidence of MACE over a 5-year follow-up period [35]. In addition, based on the results of REDUCE-IT, the combination of 4 g/day of EPA with statins contributed to a significantly lower incidence of CV events [9]. This finding provides a strong rationale for prescribing EPA to patients with HTG treated with statins [36,37].

The results of an RCT conducted among a high-risk group of patients with ASCVD demonstrated that patients treated with IPE had lower TG levels and a reduced risk of ASCVD [9]. In addition, EPA metabolites prevented hyperglycemia and hyperinsulinemia [15]. The results of experimental studies have shown that IPE protects against IGT, IR, and β-cell dysfunction caused by a high-fat diet (HFD) [38]. Among patients treated with statins in the...
REDUCE-IT Trial, IPE reduced TG levels and the risk of a first CV event by 30% compared with placebo [37]. One of the significant benefits of using IPE is reported to be an impressive 53% reduction in the risk of T2D [39].

Al Rijjal et al. [38] tested the potential protective effects of ω-3 PUFAs. It has been demonstrated that mice treated with IPE have significantly reduced TG content in the liver. The polymerase chain reaction analysis showed that the expression of peroxisome proliferator-activated receptor-alpha (PPAR-α) increased significantly in the IPE-HFD group, with a significant increase in cytochrome P450, family 4, subfamily a, polypeptide 31 (Cyp4a31), a gene for fatty acids (FA) oxidation. Thus, IPE increases the expression of PPAR-α and CYP4a31, which probably leads to increased FA oxidation, decreased liver TG levels, and reduced IR. The synthesis of ω-3 PUFAs, particularly ω-3, ω-6, DHA, is regulated by fatty acid desaturases (FADS). FADS1 gene mutations can lead to various inflammatory diseases due to changes in PUFA levels. N. Khankari et al. [39], in a multistage analysis using two-sample Mendelian randomization (MR), used large-scale European summary statistics from genome-wide association studies to assess changes in lipid levels or the risk of T2D caused by tissue-specific predicted gene expression. The results of two-sample, inverse variance-weighted MR demonstrated that FADS1-predicted increases in circulating EPA were associated with a 23% reduction in T2D risk. The authors believe that IPE via increased expression of the FADS1 gene contributes to a decrease in the level of TG, which is associated with a significant decrease in the risk of T2D.

### 3.4 Icosapent ethyl and insulin resistance

Ω-3 PUFAs may contribute to the reduction of IR through multiple mechanisms, as the effectiveness of TG reduction is associated with decreased glucose metabolism. A meta-analysis of 45 RCTs found that ω-3 PUFAs improve lipid profiles, glycemic control and lower TNF-α and interleukin-6 levels [31]. After one week, IPE reduced IR, circulating insulin, pre-prandial blood glucose (PPBG), and IGT in db/db mice. IPE was found to enhance pancreatic β-cell function, lower liver TG levels, and modify microbiota composition [38]. According to observational studies, ω-3 PUFAs have both beneficial and negative effects on glucose metabolism and T2D risk [40; 41]. In a meta-analysis of 83 RCTs, T. Brown et al. [42] examined the effects of ω-3 and ω-6 PUFA intake in 121070 individuals at risk of T2D. The study found that increasing dietary ω-3, ω-6, or total PUFAs does not prevent T2D or impact HbA1c, PPBG, or insulin levels. However, the results of the JELIS Study demonstrated the benefits of EPA ethyl ester in preventing ASCVD [35]. The reduction in T2D risk linked with IPE may only be seen in HFD [38]. Although IPE was unrelated to T2D primary prevention, REDUCE-IT observed a significant reduction in ASCVD risk, suggesting a synergistic interaction between statins and IPE [41,39]. RCTs have not proven the benefits of increasing ω-3 PUFA intake for IR patients, possibly due to poor control, a focus on treatment rather than prevention, and neglect of genetic polymorphism [43].

### 3.5 Icosapent ethyl and type 2 diabetes mellitus

IPE can contribute to the reduction of IR by alleviating OS, having anti-inflammatory effects, reducing the accumulation of FA in the liver, modulating transcription factors involved in lipid metabolism and FA oxidation, and suppressing adipocytokine production [11,27,28]. However, systematic reviews and meta-analyses have shown that ω-3 PUFAs or seafood consumption by patients with T2D do not affect biomarkers of glucose or insulin homeostasis, including HbA1c, PPBG and postprandial glycemia [17,42,31]. The discrepancies in the results obtained can be partially explained by the effect of the dosage and composition of PUFAs [38].

A. Pal et al. [15] found that IPE prevents hyperinsulinemia and hyperglycemia in C57BL/6J mice. In particular, IPE abolished the decrease in the content of 18-hydroxy EPA (18-HEPE) in white adipose tissue and the liver. The use of RvE1, a metabolite of 18-HEPE, but not 18-HEPE, in obese inbred mice abolished hyperinsulinemia and hyperglycemia via the G-protein-coupled receptor ERV1/ChemR23. RvE1 belongs to the family of endogenous PUFA metabolites known as specialized pro-soluble mediators, which actively support the physiological course of inflammatory reactions [44,19,22]. The effect of RvE1 on hyperinsulinemia and hyperglycemia differs in different animals when modeling and analyzing the human genetic polymorphism. Analysis of single nucleotide polymorphism further confirmed significant genetic variations in the human RvE1/EPA metabolic genes [45]. Taken together, these data suggest that EPA, in part through activation of RvE1 by the ERV1/ChemR23 receptor, prevents hyperinsulinemia and hyperglycemia [15]. In addition, activation of ERV1/ChemR23 by RvE1 inhibits signal transduction through the chaperone, adiponectin, which binds ERV1/ChemR23 [46].

### 3.6 Icosapent ethyl: impact on the intestinal microbiota
The results of RCTs with the use of a sardine diet (100 g of sardines for 5 days a week for 6 months, which provides approximately 3 g of EPA and DHA per day) in patients with T2D indicate a significant decrease in the Firmicutes/Bacteroidetes ratio [47]. Eight weeks of ω-3 PUFA supplementation in volunteers resulted in a consistent and reversible increase in the gut microbiome producing short-chain FA [48,49]. However, it should be noted that short-term dietary interventions cannot change the dominant individual variability of gut microbiomes. ω-3 PUFAs will likely attenuate hyperglycemia and IR and affect the gut microbiome and metabolites that link the gut to adipose tissue, the liver, and the pancreas. Thus, ω-3 PUFAs, due to favorable changes in the gut-organ axis, may be useful for restoring glucose homeostasis [40].

3. 7 IPE and risk of T2D

RvE1 protects against pro-inflammatory gene upregulation, which may lessen hyperglycemia and T2D risk. IPE’s effects can occur regardless of predicted glucose and/or insulin levels; integration of IPE into the phospholipid bilayer preserves cell membrane fluidity; and GPR binding improves insulin sensitivity and protective intestinal microbiome [15,50,38,39]. Increased erythrocyte membrane fluidity increases glucose transport and insulin signaling [51]. FADS1 protein enhances ω-PUFA incorporation into liver cell membranes in a ω-3 PUFA-rich environment [52]. IPE may reduce T2D risk by increasing erythrocyte membrane fluidity [39].

Jiang et al. [53] estimated the relative risk and 95% confidence interval of T2D, ASCVD, stroke, and death from α-linoleic acid (ALA), EPA, docosapentaenoic acid (DPA), and DHA using a random effects model. The analyses of 67 prospective trials, which enrolled 310,955 participants, were performed. A substantial adverse connection was found between ALA, EPA, and DHA and T2D risk. Biomarkers of marine ω-3 PUFAs, but not ALA, significantly reduced ASCVD risk and death. Increased EPA, DPA, or DHA biomarkers reduced ASCVD risk in a dose-response manner. The data support the importance of ω-3 PUFAs in reducing the incidence of ASCVD and early death.

4. Summary

There is strong evidence that ω-3 PUFAs effectively prevent T2D. Anti-inflammatory, antioxidant, and anti-apoptotic effects and autoimmune suppression have been demonstrated in preclinical studies [36,54,55]. DHA has neuroprotective properties. However, its use in ASCVD therapy is restricted. Instead, JELIS [35] and REDUCE-IT [37] found that long-term EPA use reduces CV incidents. The STRENGTH (Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia Trial) (EPA+DHA) outcomes are opposite [56]. A population-based research of 392,287 persons found that ω-3 PUFA intake reduces the incidence of T2D [17].

According to experimental research, genetic variation, T2D medications, and compensatory mechanisms due to dysmetabolism can affect RCT results [57,58,40,45].

Detailed descriptions of ω-3 PUFAs’ pathophysiological features rely on in vitro dose-dependent acute effects, generally employing genetically engineered models [27]. Additionally, examining the influence of a single “pharmacological substrate” is becoming outmoded. Research on the protective effects of ω-3 PUFAs in T2D, their interactions with other drugs, and daily recommendations for patients require large cohort studies using advanced metabolomics techniques and analysis, monitoring pro-/anti-inflammatory molecules, and pro-/antioxidant balance [36,59-61].

The EPA-RvE1 axis helps maintain insulin and glucose levels, possibly preventing ASCVD. Further investigations are needed to prevent and treat T2D, taking genetic variations in RvE1 and other EPA metabolites into account [15].

The RESPECT-EPA trial ongoing in Japan enrolled patients with low EPA/AA ratio, randomized to highly purified EPA (1800 mg/day) or control group [10]. After this trial is completed, new information will be released, including whether EPA decreases subsequent CV events and whether the EPA/AA ratio predicts future CV events.
References


