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Omega-3 Fatty Acids

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Indications

Omega-3 fatty acids (OM3FAs) are unsaturated fatty acids with at least one double bond located between the third and fourth omega end carbon. Currently, the *three most clinically relevant omega-3 polyunsaturated fatty acids (PUFAs) are:*

- α-linolenic acid (ALA)
- eicosapentaenoic acid (EPA)
- docosahexaenoic acid (DHA)

Oils containing these fatty acids originate in plant sources and can be found in fish, fish products, seeds, nuts, green leafy vegetables, and beans.[1][2]
Currently, the FDA has approved the use of *two prescription omega-3 fatty acids products:*

- icosapent ethyl (**Vascepa)** Contains only EPA
- omega-3-acid ethyl esters. (**Lovaza)** Contains both EPA & DHA

Iosapent ethyl and omega-3-acid ethyl esters are approved for adults (≥18 years of age) with high triglycerides as an adjunct to diet to decrease triglyceride levels and reduce cardiovascular events.[4][5][3][6] These prescription OM3FA products have also been recommended in adjunctive therapy in combination with statins to provide an enhanced reduction of the total cholesterol/high-density lipoprotein cholesterol in comparison to statin alone.[7][8][9] However, some studies have urged physicians to proceed with caution when prescribing a statin/DHA OM3FA combination due to the possibility of increased low-density lipoprotein (LDL) cholesterol.[7][10][11] DHA containing OM3FA can be switched to EPA-only icosapent ethyl that is not associated with increased LDL.[10][11]

It is important to note that while these prescription OM3FA products are the only FDA approved products for the treatment of hypertriglyceridemia, *ongoing research is currently investigating the significance of OM3FAs and their promising role in the treatment of conditions and ailments listed below:*

- Cardiovascular disease[1][12][13][14]
- Hypertriglyceridemia (200 to 499 mg/dL)[4]
- Type 2 diabetes[1]
- Cancer[1][15][16][14]
- Alzheimer disease and dementia[1]
- Depression[1]
- Visual and neurological/brain development[1]
- Maternal health during pregnancy and child health[1]
- Conditions benefiting from prebiotics[17]
- Heart failure[18][13]
- Intervertebral disc degeneration[19]
- Attention deficit hyperactivity disorder[20][21]
- Maternal depression[22]
- Menopausal night sweats[23]
- Rheumatoid arthritis[1][14]
- Asthma[24][25][14]
- Periodontal disease[1][26]
- Epilepsy[27][28]
- Diabetic retinopathy[2][29]
- Efficacy, tolerability, and side-effects of chemotherapy[30][1][31]
- Premenstrual syndrome[32]
- Non-alcoholic fatty liver disease[33]

Omega-3 intake and/or supplementation have been shown to be beneficial in treating the above conditions; however, much controversy still exists in many of the above uses. More research with well-conducted clinical trials will need to be completed before definitive conclusions can be made.

Mechanism of Action

The mechanism of action of OM3FAs to lower triglycerides (FDA approved use) is still not fully known but is thought to lower triglycerides by suppressing lipogenic gene

expression, increasing beta-oxidation of fatty acids, increasing the expression of lipo-protein-lipase (LPL), and influencing total body lipid accretion.[34][35][36] OM3FAs suppress lipogenic gene expression by decreasing the expression of sterol regulatory element-binding protein 1c, inhibiting phosphatidic acid phosphatase, and acyl-CoA:1,2-diacylglycerol acyltransferase (NGAT). Sterol regulatory element-binding proteins (SREBP's) are membrane-bound enzymes that, when cleaved, travel to the nucleus to transcribe enzymes involved in cholesterol, LDL, and fatty acid synthesis. When a diet is high in omega-3 fatty acids, the SREBPs (particularly 1c) are not activated because of negative feedback inhibition and lowers SREBP synthesis and the cholesterol synthesizing enzymes that it regulates; FPP synthase (farnesyl diphosphate synthase) and HMG-CoA reductase (3-hydroxy-3-methylglutaryl-CoA reductase).[37][38]

Beta oxidation is the biological pathway used in the body to break down fat and converts it into energy.[35]OM3FAs decrease the level of triacylglycerides in the body by increasing the rate of beta-oxidation by acting specifically on carnitine acetyltransferase 1 (CAT 1) and acetyl-CoA carboxylase.[34][35] Carnitine acetyltransferase acts to modify fatty acid substrates to enter the inner mitochondrial membrane via the carnitine-acylcarnitine translocation properly. Later, it is converted to acyl-CoA, a precursor substrate to acetyl-CoA used to create ATP in various metabolic pathways.[35] Additionally, EPA also indirectly increases beta-oxidation by slowing feedback inhibition.[35] EPA inhibits acetyl-CoA carboxylase, which is the enzyme that catalyzes the synthesis of malonyl CoA, a strong inhibitor of CAT1.[35] By decreasing the amount of malonyl CoA produced, CAT1 will have increased activity and use more triacylglycerides for beta-oxidation. OM3FAs have also been shown to decrease the sensitivity of CAT1 to malonyl CoA.[35]

Lipoprotein lipase (LPL) is an extracellular enzyme found on the endothelium of vascular tissue that functions to remove triacylglycerol components of chylomicrons, low-density lipoproteins (LDL), and very-low-density lipoproteins (VLDL) in the blood.[39][40][41] A diet high in OM3FAs has been shown to increase the expression of LPL and subsequent lipoprotein lipase protein on the endothelial lining and a decrease in the size of chylomicrons.[42] By increasing the amount of lipoprotein lipase and decreasing LDL, VLDL, and chylomicron size, triglycerides can be lower in hypertriglyceridemia patients.

OM3FAs are also believed to reduce high triglycerides by influencing total body lipid accretion. Several studies have found that prolonged use of OM3FAs for more than six weeks can increase the body's metabolic rate and decrease total body fat.[43][35][44]. More specifically, study participants showed an increase in lean muscle mass, decreased fat mass, an increase in resting metabolic rate, increased energy expenditure during exercise, and increased fat oxidation both during rest and exercise.[43][35][45][44]

On a cellular level, this is caused by OM3FAs ability to act as a ligand for peroxisome proliferator-activated receptors (PPARs), whose transcription factor activity can change gene expression involved in energy homeostasis.[43][46] PPARs regulate both fatty acid metabolism (beta-oxidation) and glucose metabolism and can change the basal metabolism of the cell.[47] The increase in fat oxidation and energy needs by changes in body composition is thought to be another mechanism by which OM3FAs help lower the triglyceride levels in the blood.

Additional mechanisms of action appear to exist for OM3FA's that explain the **beneficial effects on the brain, brain development, cancer, diabetes, rheumatoid arthritis, irritable bowel disease, and the cardiovascular system outside of triglyceride regulation.** Most of these effects are **attributed to OM3FAs' anti-inflammatory actions.** Omega-3 Fatty Acids have been shown to modulate several inflammatory pathways such as[18][48][15][49][50]:

- Inhibition of leukocyte chemotaxis
- Inhibitions of adhesion molecule expression (like leukocyte-endothelial adhesive interactions)
- Inhibition of cyclooxygenase (COX) activity and its subsequent eicosanoid production, like leukotrienes and prostaglandins from arachidonic acid
- Inhibition of proinflammatory cytokines (e.g., TNF-alpha, IL-1, IL-6)
- Increase production of inflammation resolving resolvins, maresins, lipoxins, and protectins
- Inhibition of pro-inflammatory transcription nuclear factor kappa B (nuclear factor-kB) activation
- Activation of anti-inflammatory transcription factor NR1C3
- Activation of PPARs
- Activation of G protein-coupled receptor GPR120
- Altering phospholipid fatty acid composition
- Disrupting lipid rafts

Although **many cancers** are helped by OM3FAs anti-inflammatory effect and non-small-cell lung cancer tumor growth has shown to decrease by inhibiting acetyl-CoA carboxylase (decreasing fatty acid production), other antineoplastic mechanisms of OM3FAs have been shown to be beneficial for other cancers, such as breast cancer, colorectal cancer, leukemia, gastric cancer, pancreatic cancer, esophageal cancer, prostate cancer, head and neck cancer, as well as lung cancer.[51][15] OM3FAs activate AMPK/SIRT, which is involved in cell maintenance and repair, producing an antineoplastic effect that is useful in cancer treatment.[50][15]

OM3FAs have a stabilizing and protecting effect for certain tissues with high-fat content, like neural and retinal tissue. **Alzheimer disease, dementia, and cognitive function** are improved by OM3FAs ability to maintain cell membrane integrity of neural tissues because DHA is an essential component of the brain's phospholipid membranes.[52][53][54] Additionally, **macular degeneration** can be helped with the supplement of DHA for structural support and EPA-based eicosanoids for neovascular and cell survival because DHA and EPA are also integral components of retinal cell membranes.[55]
OM3FAs have some **cardioprotective effects** that help protect against heart failure in congestive heart failure (CHF) patients. OM3FAs, specifically DHA, decrease mitochondrial oxygen consumption without reducing power generation for the ventricles by altering the mitochondrial membrane phospholipid composition, protecting the heart from tiring.[18] Whereas EPA inhibits the apoptotic activity stimulated by saturated fatty acid cardiac lipotoxicity, protecting the heart from injury.[18] OM3FAs can protect from arrhythmia by inhibiting inward sodium current in a dose-dependent manner, suppressing intracellular calcium (Ca2+) waves, and helping strengthen autonomic tone.[56] OM3FAs can also **vasodilate and decrease blood pressure** or afterload to help the heart pump easier because they stimulate nitrous oxide (NO) release from vascular endothelial tissue.[18] OM3FAs also protect the heart through their **antithrombotic and antiatherosclerotic abilities**. OM3FAs have been shown to suppress platelet-derived thromboxane A2 (TXA2) synthesis, which constricts blood vessels and aids in platelet aggregation, and reduces the production of matrix metalloproteinases released by macrophages when there is endothelial injury.[18][57]
It should be noted that numerous studies continue to determine the exact mechanisms by which OM3FAs have a pharmacological effect. Many studies with conflicting data

continue to challenge our current understanding of how OM3FAs can help other conditions beyond hypertriglyceridemia.

Administration / Dose

The FDA-approved uses of omega-3 fatty acids for adults (≥18 years of age) with hypertriglyceridemia (≥ 500 mg/dl) as an adjunct to diet and exercise are as follows[3][4][6]:

- **Icosapent ethyl** (VASCEPA) is administered as capsules with a daily dose of 4 g/day taken as two, 2-gram capsules twice a day with meals.
- **Omega-3-acid ethyl esters** (LOVAZA) are administered as capsules with a daily dose of 4 g/day taken as 4 capsules once a day with meals or two capsules twice a day with meals.
- **Omega-3-carboxylic acids** (EPANOVA) are administered as capsules with a daily dose of 2 g/day taken as 2 capsules once per day or 4 g/day taken as 4 capsules once a day. Clinical trial administration was without regard to meals.

All OM3FA supplements should be taken whole without being crushed, chewed, or dissolved in the mouth. If a dose is missed, the patient should take it as soon as they remember and should not take a double dose if it is time for their next capsule. Various dietary supplements in different chemical forms are currently available over the counter but have not been FDA approved; hence they are not required to show safety and efficacy before marketing the product.[3]

Metabolism

Humans do not possess the enzymes required to synthesize OM3FAs; therefore, they are considered essential fatty acids because they must be obtained from the diet. OM3FAs are mainly consumed in our diets as fish and plant sources but can also be consumed via prescription OM3FA products.[58] Alpha-linoleic acid (ALA) is a common OM3FA found in seeds and nuts and can be converted to both DHA and EPA inside the body. However, research has found the conversion of DHA from ALA is particularly low, suggesting the importance of direct dietary intake of DHA.[1][59] OM3FAs may be present in several forms, such as triacylglycerols, free fatty acids (FFA), phospholipids, and ethyl esters.[1] Icosapent ethyl, omega-3-acid ethyl esters, and omega-3-acid ethyl esters A are all in the ethyl ester form, whereas; omega-3-carboxylic acids are in the free fatty acid form.[6]

Digestion of OM3FAs begins in the stomach with gastric lipases that break down triacylglycerols into diacylglycerol and fatty acids.[1] Once broken down, they form fat globules that are subsequently broken down by pancreatic lipases and bile salts in the small intestines. The ethyl esters (icosapent ethyl, omega-3-acid ethyl esters, and omega-3-acid ethyl esters A) are principally broken down by pancreatic carboxylic acid ester lipase in the small intestine to form FFA-EPA and FFA-DHA.[1] Monoacylglycerols and the free fatty acids then passively diffuse into enterocytes as micelles.[1] Fatty acids can also be transported into enterocytes by various fatty acid transport proteins present in the enterocyte membrane.[60] Once within the enterocyte, the fatty acids are then re-esterified into triacylglycerols in the endoplasmic reticulum that then bind to apolipoproteins to form chylomicrons.[1][60] Chylomicrons are subsequently exocytosed into the lymphatic system and ultimately enter circulation at the thoracic duct to reach target tissues.[1][60]

While most metabolism of DHA and EPA takes place via beta-oxidation in the liver (as discussed above), cytochrome P450 (CYP)-mediated metabolism is a minor pathway in the breakdown of DHA and EPA.[61]

Bioavailability

In the digestion process, the ethyl esters are principally broken down by pancreatic carboxylic acid ester lipase, an enzyme with activity enhanced by high-fat content meals.[1] Moreover, the fat content of a meal can affect the absorption of ethyl esters.[1] Subsequently, absorption of the ethyl esters and icosapent ethyl (EPA formulation only) is decreased when fasting, so it is recommended they are consumed with food.[4] Regarding the absorption of EPA versus DHA, it is thought that EPA is not absorbed as well as DHA and is metabolized faster; thus, there is a higher ratio of DHA to EPA within the serum plasma.[60]

Since OM3FAs may be present in several forms, such as triacylglycerols, free fatty acids, phospholipids, and ethyl esters, the form in which the OM3FA acid is in will affect bioavailability.[1] The suggested bioavailability based on form (lipid structure) from highest to lowest is as follows: phospholipids, re-esterified triacylglycerols, triacylglycerols, free fatty acids, ethyl esters.[58] However, the order is based on lipid structure only and does not reflect other factors that affect the bioavailability OM3FAs, such as the fat content of a meal.[58]

In addition to the form of the OM3FA, the chemical positioning may also affect bioavailability. Some research suggests OM3FA is greater in fish oil due to the OM3FA typically being in the sn-2 position versus marine mammal oils with the OM3FAs in the

sn-1 and sn-3 positions.[58][1] Conversely, other sources state that OM3FAs bioavailability is increased in the sn-1 and sn-3 position due to increased accessibility for lipase hydrolysis, so controversy remains regarding how the position affects the bioavailability of the OM3FAs.[58][60] Bioavailability also varies depending on the dietary source. For example, krill oil is known to have high bioavailability compared to other marine sources.[58][60]
Bioavailability of EPA only and both EPA/DHA formulations did not differ based on age or ethnicity; however, the combination formulation bioavailability differed based on gender. Women seem to have higher EPA serum levels than males in the mixed EPA/DHA formulations. However, research on the availability of EPA and DHA of over-the-counter supplements has indicated that age can play a factor in their levels within the plasma.[60] It has also been found that serum EPA increases in a dose-dependent manner when administered with ethyl esters, but serum DHA does not.[6]

Half-Life

Not all of the half-lives of the prescription OM3FA products have been established. The maximum amount of plasma EPA and DHA can be determined within five to nine hours post-administration.[58] However, *persistent EPA and DHA serum levels will not be apparent until two weeks of daily supplementation*.[58]With repeated administration, the half-life of EPA is 37 hours and 48 hours for DHA.[58]

Adverse Effects

The FDA-approved fatty acid prescriptions (icosapent ethyl, omega-3-acid ethyl esters,omega-3-carboxylic acids, and omega-3-acid ethyl esters A) are generally safe with benign side effects such as fishy taste, eructation, dyspepsia, diarrhea, gas, nausea, and arthralgia.[4][62][63]
Adverse reactions seen in clinical trials for each of the FDA approved OM3FA products are as follows[4][3][6]:

- **Icosapent ethyl:** arthralgia and oropharyngeal pain.
- **Omega-3-acid ethyl esters:** eructation, dyspepsia, taste perversion, constipation, GI disorder, vomiting, increased ALT/AST, pruritus, rash.
- **Omega-3-carboxylic acids:** Diarrhea, nausea, abdominal pain or discomfort, eructation, abdominal distension, constipation, vomiting, fatigue, nasopharyngitis, arthralgia, dysgeusia.

Contraindications

Caution and periodic monitoring are recommended in patients taking antiplatelet and anticoagulant medication due to the ability of omega-3 fatty acids to reduce platelet activity.[4][15] Additionally, omega-3 fatty acids are not considered allergenic, but the FDA labels state to use with caution in patients allergic to seafood. The OM3FAs products are contraindicated for those who have hypersensitivity to the individual formulation.[4]

EPA and DHA can act as alternative substrates for CYP450 metabolism and are partially metabolized by the CYP450 metabolic pathway, however significant inhibition of CYP450 enzymes by DHA or EPA has not been observed and no drug-drug interactions have been established with medications that use the CYP450 metabolic pathway. EPA exclusive supplements have shown to have no drug-drug interactions with other medications that may use the P450 metabolic pathway, such as omeprazole, warfarin, atorvastatin, and rosiglitazone. DHA has shown to have no interactions with other statin drugs.