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REVIEW **DERLEME**

THE USE OF FISH OILS FOR VASCULAR HEALTH

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ABSTRACT

The role of dietary interventions and use of supplements to protect or improve vascular health has been an ongoing research topic for many years. In this context, one of the most frequently discussed topics is fish oils. Both the diversity in its chemical structure and the difference in its composition either obtained from natural sources or offered as supplements make it difficult to understand the possible benefits of fish oil in vascular health. In this review, it is aimed to summarize the terminology related to the concept of fish oil and discuss the most recent information and discussions of its use in the field of vascular health, with a specific emphasis on the differences between the commercially available preparations.
Keywords: Fish oil, omega-3 and omega-6 fatty acids, nutrition, cardiovascular health.

VASKÜLER SAĞLIK İÇİN BALIK YAĞI KULLANIMI

ÖZ

İnsanların vasküler sağlığının korunması veya iyileştirilmesi için beslenme ile ilgili çeşitli alışkanlıkların değiştirilmesi ve gıda takviyelerinin kullanılmasının rolü çok uzun yıllardan bu yana devam eden bir araştırma konusudur. Bu bağlamda en çok gündeme gelen başlıklardan bir tanesi balık yağlarıdır. Gerek kimyasal yapısındaki çeşitlilik, gerekse doğal kaynaklardan elde edilen veya takviye olarak sunulan preperatlardaki farklılık balık yağının vasküler sağlıktaki olası faydasının anlaşılmasını zorlaştırmaktadır. Bu derlemede balık yağı kavramı ile ilgili terminoloji, kullanılan preperatlar arasındaki farklılıklar ve vasküler sağlık alanındaki en güncel bilgi ve tartışmaların özetlenmesi amaçlanmıştır.
Anahtar Sözcükler: Balık yağı, omega-3 ve omega-6 yağ asitleri, beslenme, kalp damar sağlığı.

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The connection between fish oil and vascular health has been a subject of extensive discussion from different aspects across diverse specialities, primarily cardiology and neurology. Epidemiological observations of a reduced occurrence of cardiovascular events since the 1930s in populations like Eskimos, or Scandinavian communities, , who consume notably higher quantities of oily fish compared to Western diets, have prompted consideration of fish oil as a preventive and potentially therapeutic intervention for various conditions caused by atherosclerosis, including myocardial infarction, stroke, and peripheral arterial disease (1-5).

Before delving into the protective or therapeutic implications of fish oils for vascular health, it is crucial to grasp the terminology used in this context, ensuring an accurate analysis of the available literature. Fish oils belong to the fatty acid family, which includes wide range of chemical structures and diversity. Fatty acids, formed by bonding carboxylic acid to specific lengths of aliphatic chains, possess a characteristic of blending hydrophobic and hydrophilic properties, thereby effectively combining water-insoluble and soluble chemical structures. This amphipathic structure grants fatty acids distinct attributes, including their role as fundamental constituents of cell membranes and as water-soluble, high-energy reservoirs. Furthermore, as elaborated below, the variability within the fatty acid family empowers this chemical composition to participate in essential bodily functions such as energy pathways, signaling mechanisms, inflammation responses, and gene transcription.

Describing the terminology of the fatty acid family can be complex due to its diversity. When chemically defining a fatty acid, several characteristics need to be taken into consideration:

a. Chain length: The length of the aliphatic chain, or in other words, the number of carbon atoms it contains, is a fundamental descriptor of a fatty acid. Fatty acids can be categorized based on chain length: short-chain fatty acids contain 5 or fewer carbon atoms, medium-chain fatty acids range from 6 to 12 carbon atoms, long-chain fatty acids encompass 13 to 21 carbon atoms, and very long-chain fatty acids have 22 or more carbon atoms.

b. Saturation: The presence of double bonds between carbon atoms within the aliphatic chain is the second aspect to consider when defining fatty acids. Fatty acids are classified as either saturated or unsaturated based on the presence of these double bonds. If all carbon-carbon bonds along the aliphatic chain are single bonds, the fatty acid is saturated; if one or more double bonds exist, it's unsaturated. Fatty acids with a single double bond are called monounsaturated, and those with multiple double bonds are referred to as polyunsaturated. Saturated fatty acids have single bonds between carbon atoms, allowing the carbons to move freely in a three-dimensional plane and form a compact structure within their flexible configuration. As a result, most saturated fatty acids are solid at room temperature. On the other hand, the double bonds in unsaturated fatty acids restrict rotation in various directions, leading to folding when visualized in three dimensions. This reduced flexibility prevents the formation of a compact structure when multiple unsaturated fatty acids come together, causing them to typically exist as liquids at room temperature.

c. Isomeric structure: This terminology primarily pertains to unsaturated fatty acids. Saturated fatty acids form two bonds with neighboring carbon atoms and attach two hydrogen atoms to each carbon atom. In contrast, unsaturated fatty acids, which include one double bond, have one remaining binding site for a single hydrogen atom. When two hydrogen atoms bonded to the carbon atoms connected by the double bond are on the same side, it's referred to as the "cis" isomer, whereas when they are on opposite sides, it's termed the "trans" isomer. In trans isomers, the hydrogen atoms are positioned on opposite sides, allowing for a flexible and compact structure similar to saturated fatty acids. In contrast, the arrangement of hydrogen atoms in cis isomers makes it challenging for them to exist within a compact structure (Figure).

d. Position of the double bonds: This terminology is inherently related to unsaturated fatty acids. The position of the double bond can be counted from where the carboxylic acid is located or counted backward from the end of the aliphatic chain. While the first method is more commonly used in chemical terminology, the second method is often applied in clinical and practical contexts. In the second method, the carbon at the very end of the aliphatic chain is termed the omega (ω) carbon, and the naming is based on the carbon where the first double bond is present when counted backward (ω-3 or ω-6, for example) (Figure). In this context, a separate discussion is needed for ω-3 and ω-6 fatty acids. Among the well-known fatty acids playing vital roles in bodily functions, alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are notable examples of ω-3, while linoleic acid and arachidonic acid represent ω-6 fatty acids.

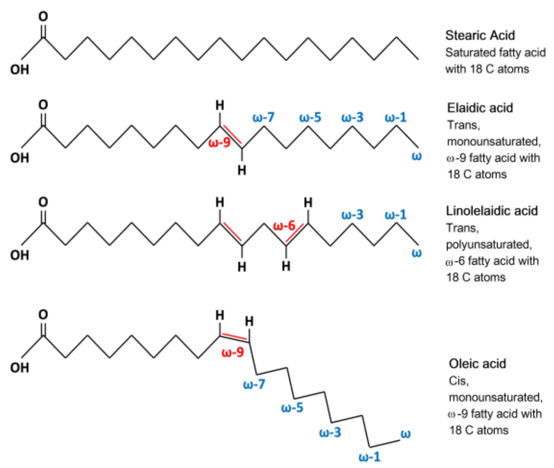

Figure. Fatty acid terminology.

After this comprehensive and elaborate introduction, when we refer to fish oil, we are actually talking about all the combinations of fatty acids obtained from oily fish. These oils, predominantly sourced from cold-water fish like herring, sardines, mackerel, salmon, or tuna, contain high amounts of long-chain, polyunsaturated fatty acids (PUFAs) with numerous double bonds in the cis isomer formation. While the composition of fish oils varies based on the fish they are derived from, the ratio of ω-3 to ω-6 fatty acids generally falls within the range of 6 to 7.

Both ω-3 and ω-6 fatty acids have been extensively studied in the literature for their effects on vascular health. These studies utilize various methods, including observational studies that meticulously evaluate dietary habits, randomized trials with modified diet contents or dietary supplements, and investigations measuring blood levels of relevant fatty acids. While not all studies unanimously support these findings, data suggests that ω-6 fatty acids, particularly due to their LDL-lowering and blood pressure-reducing effects, may mitigate the overall risk of cardiovascular events, including stroke (6,7). Similarly, although not universally endorsed across the literature, there are signals indicating positive effects of ω-3 fatty acids on cardiovascular health, attributed to mechanisms such as lowering triglyceride levels, enhancing endothelial function, and reducing inflammation (8-10). However, just like in various other nutrition-related studies, significant heterogeneity and inconsistency among the results of fatty acid-related studies lead to a lack of clear consensus on the prophylactic or therapeutic use of ω-3 or ω-6 supplementation.

Various factors contribute to these inconsistent observations; however, critical points for discussion arise from individuals' dietary habits and the definition of the control group. Human dietary habits have undergone dramatic changes throughout evolutionary processes and the past century's modern lifestyle. Amid this transformation and increased prevalence of the Western-style diet, total fat intake has risen, the ratio of saturated and unsaturated fats has skewed in favor of saturated fats, intake of trans fats has surged – which are well-acknowledged for their vascular harm – and the content of polyunsaturated fatty acids (PUFAs) in the diet has decreased. Epidemiological studies undeniably highlight that enriching dietary habits with beneficial fatty acids, including ω-3 and ω-6 PUFAs, improves vascular health. Nevertheless, questions concerning the daily grams of ω-3 or ω-6 to be consumed for medical nutrition purposes, the necessity and methodology of dietary supplementation in achieving these targets, remain unresolved.

Especially within the context of ω-3 supplementation, the ongoing debate is intensified by the specific combination of fatty acids provided in these supplements. While the ω-3 family generally exhibits consistent triglyceride-lowering effects, their impact on LDL differs: EPA doesn't significantly alter LDL levels, while DHA can increase LDL levels, thereby potentially reducing the vascular benefits theoretically achieved through ω-3 supplementation (11). Despite statistically significant positive effects on cardiovascular outcomes in randomized trials employing pure EPA supplementation (such as REDUCE-IT, JELIS, EVAPORATE), neutral results observed in studies combining EPA and DHA (STRENGTH, VITAL, ASCEND, and OMEMI) suggest that these two molecules may exert distinct effects on lipid levels (Table) (12-19). On the other hand, the debate rages on whether the positive results seen in REDUCE-IT and EVAPORATE stem from the daily 4-gram dose of EPA supplementation or from the mineral oil given to the control group, which led to an increase in LDL levels. Moreover, preliminary evidence suggesting that high-dose ω-3 supplementation examined in these studies may elevate atrial fibrillation frequency adds more uncertainty to the realm of fatty acid dietary supplements (20,21).

In conclusion, a clear and consistent body of evidence supporting the use of fish oils as dietary supplements for vascular health is yet to emerge. While positive outcomes have been observed with pure EPA supplementation, ongoing discussions about control group matters, and the potential atrial fibrillation side effect raised in recent years, keep questions afloat in this field. Nevertheless, setting aside the discussions on medical supplementation, enriching dietary habits to include polyunsaturated fatty acids – including those from fish oils –, reducing trans and saturated fat intake, and switching to a diet that shifts the ω-6: ω-3 balance in favor of ω-3, is widely recognized as having positive effects on vascular health.

Table. Randomized trials evaluating the effects of ω-3 fatty acids on vascular health.

Study	Treatments Used	Primary Endpoint	Conclusion
REDUCE-IT, 2019 (12)	2x2 g icosapent ethyl vs mineral oil	cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, unstable angina	17.2% vs. 22% [HR 0.75 (0.68-0.83); p<0.001] Follow-up time: 4.9 years
JELIS, 2007 (13)	1.8 gr EPA vs. nothing	Sudden cardiac death, fatal and non-fatal myocardial infarction, angina pectoris, angioplasty, stent, coronary by-pass surgery	2.8% vs. 3.5% [HR 0.81 (0.69-0.95); p=0.011) Follow-up time: 4.9 years
EVAPORATE, 2020 (14)	2x2 g icosapent ethyl vs mineral oil	Low attenuation plaque volume	-0.3±1.5 vs. 0.9±1.7 mm^3; p<0.001 Follow-up time: 18 months
ASCEND, 2018 (15)	1 g fish oil (460 mg EPA / 380 mg DHA) vs. olive oil	Vascular death, non-fatal myocardial infarction, non-fatal stroke, transient ischemic attack	8.9% vs. 9.2% [HR 0.97 (0.87-1.09); p=0.55] Follow-up time: 7.4 years
VITAL, 2019 (16)	1 g fish oil (460 mg EPA / 380 mg DHA) vs inactive placebo	cardiovascular death, non-fatal myocardial infarction, non-fatal stroke	2.98% vs. 3.24% [HR 0.92 (0.80-1.06); p=0.24] Follow-up time: 5.3 years
OMEMI, 2021 (17)	1.8 g PUFA (930 mg EPA / 660 mg DHA) vs. corn oil	Non-fatal myocardial infarction, unexpected revascularization, stroke, death, hospitalization with heart failure	21.4% vs. 20% [HR 1.08 (0.82-1.41); p=0.60] Follow-up time: 2 years
STRENGTH, 2020 (18)	4 g PUFA (2.1 g EPA / 0.8 g DHA) etc., corn oil	cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, unstable angina	12% vs. 12.2% [HR 0.99 (0.90-1.09); p=0.84] Follow-up time: 42 months

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Ethics

Ethics Committee Approval: There is no need ethical approvel for this study because it is a review article.

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