REVIEW PAPER

Use of polyunsaturated fatty acids in prevention and treatment of gastrointestinal diseases, obesity and cancer (ahead of print)

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Summary

Fatty acids are important structural and functional elements of human body. We can distinguish several types: among others polyunsaturated fatty acids, which include omega-3 fatty acids (ω-3PUFA) and omega-6 fatty acids (ω-6PUFA). The first group has pleiotropic health-promoting effects, while the second group, ω-6PUFA, negatively affects the homeostasis of the human body and contributes to the development of numerous diseases. Both the amount and the relative ratio of these acids in the diet is an important factor affecting health and quality of life.

Laboratory and clinical studies indicate that ω-3PUFA have a positive effect on the therapy of illnesses such as obesity and inflammatory bowel disease (IBD). ω-3 PUFA supplementation also appears to have a helpful effect in the adjuvant treatment of colorectal cancer and recovery.

Key words: polyunsaturated fatty acids, gastrointestinal diseases, obesity, cancer

Słowa kluczowe: wielonienasycone kwasy tłuszczowe, choroby przewodu pokarmowego, otyłość, nowotwory

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INTRODUCTION

Fatty acids are one of the basic types of biological compounds. They are the building blocks of cell membranes, as well as an important source of energy for the human body. They can be divided into saturated and unsaturated fatty acids.

PUFA (polyunsaturated fatty acids), due to their health-promoting values, have recently attracted the interest of scientists. They have a double chemical bond in their structure. Depending on the position of the double bond, we distinguish two most popular groups of these acids: omega-3 and omega-6 (tab.1) according to Tvrzicka et al. [1].

<table>
<thead>
<tr>
<th>Omega-3 fatty acids (n-3 PUFA)</th>
<th>Omega-6 fatty acids (n-6 PUFA)</th>
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<tbody>
<tr>
<td>• α-linolenic acid (ALA) - the main compound of this group</td>
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<tr>
<td>• Eicosapentaenoic acid (EPA)</td>
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<tr>
<td>• Docosahexaenoic acid (DHA)</td>
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<tr>
<td>• Linoleic acid (LA) - the main compound of this group</td>
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<tr>
<td>• Gamma-linolenic acid (GLA)</td>
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<tr>
<td>• Arachidonic acid (AA, ARA)</td>
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The human body is unable to synthesize omega-3 and omega-6 essential fatty acids, ALA and LA, respectively, which is due to the lack of appropriate desaturases. In addition, compounds from these groups are necessary for proper functioning of the body. It follows that a person must provide adequate amounts of omega-3 and omega-6 acids in diet to maintain internal homeostasis [1-3].

OMEGA-3 FATTY ACIDS: FUNCTIONS AND SOURCES

The most important of ω-3PUFAs is α-linolenic acid (ALA). Its sources are seeds of some plants, e.g., black currant or flax. Indirectly, ALA is a source of the other two most important omega-3 acids - eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Another source of EPA and DHA are fish oils obtained from sardines, mackerel, salmon, tuna [4, 5]. The process of converting ALA to EPA or DHA does not provide substantial amounts of EPA or DHA, hence the main source of these two acids remains food [6].

Thanks to the influence of ALA on fluidity of cell membranes, concentration of lipoproteins in cell membranes, activity of enzymes and receptors localized in cell membranes, synthesis of eicosanoids, metabolism of minerals and lowering of arterial pressure, ALA has anticoagulant and anti-atherosclerotic properties [7]. Omega-3 fatty acids are also ligands for peroxisome proliferator-activated receptors (PPAR-α). Their action as a ligand contributes to a decrease in lipogenesis activity. They also decrease very low-density lipoprotein (VLDL) concentrations [8]. In addition, they have many other functions in the regulation of lipid metabolism: they increase lipoprotein lipase activity, decrease apo C-III concentration, and stimulate reverse cholesterol transport [9, 10].

DHA is one of the essential elements entering the structures of nervous tissue and retina. During developmental age, adequate DHA levels are extremely important for proper development of both these elements [10, 11].

Omega-3 fatty acids also influence the immune system. They modulate its activity by decreasing the activity of T lymphocytes [12].

In addition to their effect on T lymphocytes, n-3 PUFAs have a wide range of interference in the functioning of other cells of the immune system such as B lymphocytes [13], NK cells [14], macrophages [15], mast cells [16], dendritic cells [17], basophils [18] and neutrophils [19]. The exact mechanisms of the effects of omega-3 fatty acids on the aforementioned immune cells remain to be discovered. Currently, two mechanisms of regulation of immune cells by ω-3PUFAs are known: action on the cell membrane and activation of transcription factors. A more detailed understanding of the mechanisms of action of omega-3 fatty acids on immune cells will allow their use in some diseases. In animal models of diseases such as autoimmune hepatitis or sepsis, ω-3PUFA gave positive results [20]. Immunomodulatory function of omega-3 fatty acids may lead to a better treatment of diseases whose essence is the overactivation of the immune system, but the number of clinical trials in this matter is too small to draw definitive conclusions. ω-3PUFA, can be considered as prebiotics. They have a positive effect on the intestinal microbiota, thus acting to inhibit inflammatory processes taking place in the intestinal area [21].

The various functions performed by omega-3 fatty acids, makes them an important element in maintaining homeostasis in the human body. Their content in the diet is an important factor both during the development of the human body (e.g. DHA), and in later stages of life.

OMEGA-6 FATTY ACIDS

The essential acid of this group is linoleic acid (LA). High concentrations of ω-6PUFAs are present in
products such as sunflower oil, soybean oil, grape seed oil and sesame oil [22].

ω-6PUFAs are the main precursors of eicosanoids which include prostaglandins, prostacyclins, leukotrienes, thromboxanes and lipoxins [23, 24]. They are PPAR activators, more selective for gamma than alpha (γ>α), thus leading to an increase in insulin sensitivity and affecting adipocyte size and fat distribution [25]. Additionally, they contribute to increase in cholesterol synthesis, an increase in LDL receptor activity, a decrease in the conversion of VLDL to LDL, and an increase in Cyp7A1 activity [26].

Most eicosanoids synthesized from omega-6 fatty acids have a negative impact on health. Except prostaglandins, they have prothrombotic and pro-inflammatory effects. Another aspect is the fact that the pathomechanisms of many chronic diseases are associated with increased synthesis of compounds such as thromboxane A2, leukotriene B4, IL-6, TNF (tumor necrosis factor) or CRP (C-reactive protein). An increased supply of ω-6PUFAs contributes to increase in the concentrations of the above-mentioned compounds, thus contributing to disease propagation. An important indicator related to the amount of ω-6PUFAs in the diet is omega-6 to omega-3 acids ratio. Changes in the diet that have occurred over the development of civilization have led to a large change in the ratio of these acids. The human species is best adapted to 1/1 ratio, while current ratio of ω-6PUFAs to ω-3PUFAs in Western civilization diet is between 15.1/1 and 16.7/1. Such a substantial change is reflected in human health, contributing to the development of many chronic diseases [27]. Data from numerous scientific papers confirm that low omega-6 to omega-3 ratio is beneficial for human health [28]. A low ω-6PUFA to ω-3PUFA ratio contributes to lower triglyceride levels, increased HDL concentrations [29], reducing insulin resistance [30], lower concentrations of pro-inflammatory compounds such as TNF-α and IL-6 [31], reduces the risk of Alzheimer’s disease [32], reduces the risk of the development of obesity [33], reduces the risk of coronary heart disease [34], breast cancer, and colorectal cancer [35].

Typical western diet contains an excess of harmful ω-6PUFA, with too little amount of ω-3PUFA. This leads to the propagation and development of diseases, hence it is recommended to reduce omega-6 fatty acids in the diet and increase the supply of omega-3 fatty acids [27].

EFFECTS OF OMEGA-3 FATTY ACIDS ON TREATMENT OF DISEASES GASTROINTESTINAL DISEASES – INFLAMMATORY BOWEL DISEASES

Inflammatory bowel diseases (IBDs) are a diverse group of conditions with a complex pathogenesis – genetic factors, abnormal immune responses, body’s microbiome, and environmental conditions are all important. The result is an imbalance between pro- and anti-inflammatory molecules such as cytokines, interleukins, activated toll-like receptors, nitric oxide, free radicals and oxylipins. This leads to the persistence of chronic inflammation and disease symptoms such as bloating, diarrhoea, and abdominal pain, among others [36]. The treatment of these diseases is a challenge due to their recurrent nature and multifactorial and complex etiopathogenesis. Current therapy consists mainly of corticosteroids, biopharmaceuticals, immunosuppressants and antibiotics. This treatment is extremely expensive and associated with a high risk of numerous side effects, so the search for more favourable methods of treatment support is ongoing [37].

There is a lot of evidence for the correlation of diet and the intensity of inflammatory processes in people with IBD. It is important to increase fibre and vitamin D intake in diet and reduce fats and simple sugars. Much attention has also been paid to ω-3PUFAs. In 2019 meta-analysis by Mozaffari et al. it was found that consumption of ω-3PUFAs significantly reduced the risk of ulcerative colitis [38].

Several studies have shown that long-chain ω-3PUFAs delivered in the form of vegetable oils or fish oils, protect against colitis by decreasing cytokine expression, improving barrier function, reducing the expression of adhesion molecules, inhibiting the secretion of inflammatory eicosanoids, and positively altering the microbiome [39, 40]. ω-3PUFAs are also a substrate to produce protecins, resolvins and maresins, which can regulate and mitigate inflammatory processes and lead to IBD remission [41].

Studies in animal models also demonstrate the anti-inflammatory effects of ω-3PUFAs, in contrast to a high-fat diet, which causes intestinal barrier dysfunction and increased inflammation. [42, 43].

Using modern genetic sequencing techniques, researchers have discovered that the composition of the gut microbiome in IBD patients differs from that of healthy individuals [44]. Dietary habits, also important in the pathogenesis of gastrointestinal and
liver diseases [45, 46], influence the composition of the microbiome; in this matter ω-3PUFAs can also be helpful due to their positive impact on microbiota of gastrointestinal tract [21].

The number of studies suggesting the efficacy of fatty acids as an adjunct in the prevention and treatment of IBD seems to indicate their effectiveness. However, further investigation on a larger number of patients and with a greater variety of research methods is necessary.

**OBESITY**

The increase in the incidence of obesity is one of the biggest problems of modern civilization. This problem occurs in adults, but increasingly also affects children. Excessive accumulation of fat tissue is associated with numerous complications such as vascular and cardiovascular diseases, insulin resistance, diseases of the musculoskeletal system – resulting in a significant reduction in the length and quality of life.

One of key factors in preventing obesity is an appropriate and balanced diet. There is the evidence that natural fatty acids may have a positive effect on inhibiting this disease.

ω-3PUFA modulates the secretion of leptin, a protein secreted by fat cells which is responsible for the inhibition of appetite. Elevated plasma leptin concentrations have been found in obese individuals. This leads to decreased sensitivity of leptin receptors located in the hypothalamus, resulting in an increased sensation of hunger when attempting to lose weight and re-gain weight [47]. Dietary EPA supply decreases the decrease in leptin in blood, which reduces the hunger experienced by the patient and decreases the risk of re-gaining weight [48]. The dietary pattern of study participants shows a marked reduction in fat, carbohydrate, and total calorie intake after the inclusion of ω-3PUFAs [49]. It was shown that among people who consumed meals higher in ω-3 PUFAs, a sense of satiety occurred faster, reducing the overall amount of food consumed. This effect is desirable in people seeking for the reduction of body weight [50]. Additionally, ω-3PUFAs are agonists of the FFAR4 receptor, which encodes a protein that provokes the secretion of cholecystokinin, a hormone that is synthesized and released from the gastrointestinal tract and one of its functions is to inhibit hunger [51].

DHA and EPA exert hypolipidemic effects on the body – by influencing fat metabolism, they reduce the risk of insulin resistance and other complications of obesity [52]. The use of ω-3PUFAs in diet can reduce both hypertrophy and hyperplasia of fat cells. The exact mechanism has not been understood yet; one suggested approach is to promote mitochondrial biogenesis, which may increase cellular energy metabolism [53]. They also increase fatty acid oxidation and decrease lipogenesis [54].

Studies have shown that higher concentrations of saturated fatty acids in subcutaneous tissue led to increased fat cell size, while higher concentrations of ω-6 and ω-3PUFAs lead to decreased fat cell size [55]. DHA and EPA also prevent lipogenesis and stimulate fatty acid oxidation in liver in an AMPK and PPARα-dependent manner [56]. There is a proven link between BMI, body fat percentage and markers of inflammation. NF-κB, a protein complex that acts as a transcription factor in inflammatory cytokine gene expression, is inhibited by ω-3 PUFAs. Both in vitro and in humans, ω-3PUFAs have shown to be involved in the reduction of cytokines such as IL-1, IL-6, and TNF-α, elevated levels of which are found in obese individuals [57].

ω-3PUFAs increase mitochondrial oxidative capacity in skeletal muscle and subcutaneous white adipose tissue, probably through upregulation of UCP-3, the proteins that carry hydrogen ions across the mitochondrial inner membrane. However, mechanisms related to the role of ω-3PUFAs in the likely induction of energy expenditure and fat reductio should be investigated in future [58].

The Women's Health Initiative Study observed an association between ω-3PUFA, ω-6PUFA, and their ratio in red blood cell membrane phospholipids and the risk of obesity or being overweight. Higher ω-3PUFA concentrations in red blood cells were associated with a reduced risk of mortality due to weight gain, whereas high cis ω-6 concentrations, the ω-6/ω-3 ratio, and trans fatty acids correlate with weight gain and associated disadvantages [59].

**CANCER**

Increasingly, studies emphasize the importance of diet on the risk and progression of chronic diseases, including inflammatory diseases and cancer [60].

Colorectal cancer (CRC) is an aetiologically multifactorial disease. It consists both of genetic and environmental factors. Lifestyle, diet, alcohol, smoking, changes in cell signalling pathways, genetic mutations are just a few of possible risk factors for the development of this disease. The result is altered by intestinal homeostasis and tumorigenesis [61].
A 2021 meta-analysis showed the association between dietary fatty acid content and colorectal cancer risk. Higher EPA intake was significantly associated with 11% reduction in CRC risk, while high DHA intake was associated with a 12% and 13% reduction in CRC and rectal cancer risk, respectively, compared with individuals with low intakes of these fatty acids [62].

The number of laboratory and preclinical studies supporting the role of ω-3PUFAs in colorectal cancer continues to increase. Unfortunately, to date they have not been translated into clinical application. ω-3PUFAs cause increased apoptosis of cancer cells, mainly by acting on the redox state of these cells. They increase the concentration of intracellular reactive oxygen species, inducing apoptosis by mitochondrial membrane loss, increasing the Bax/Bcl2 ratio, and activating caspases 3 and 9 [63]. ω-3PUFAs can also modulate cyclooxygenase (COX) metabolism and reduce prostaglandin PGE2 production, which is a potent pro-inflammatory and pro-carcinogen - it drives pro-tumorigenic proliferation, migration and invasion, but also promotes an immunosuppressive tumor microenvironment and inhibits the apoptosis mechanism [64, 65]. Over 90% of colorectal cancers show elevated COX-2 expression [66].

However, modifying COX metabolism is not the only antiproliferative mechanism that ω-3PUFAs exhibit. At the molecular level, their involvement in the Hippo tumour suppressor pathway has been described [67]. They have also been shown to down-regulate other colorectal cancer-promoting signalling pathways, such as the Wnt/β-catenin pathway [68], the MAPK/ERK pathway [69], and the PI3K-PTEN pathway [70].

In addition, they exhibit antitumor activity by affecting the surface G-protein coupled receptors (GPCRs) of free fatty acids, which results in the activation of apoptosis [67]. GPCRs are also expressed on non-epithelial cells such as macrophages [71] and adipocytes [72], resulting in reduced inflammation.

The accumulation of ω-3PUFAs in colon cancer cells has also shown the increase of lipid peroxidation and cellular oxidative stress [73]. DHA has been shown to inhibit Granzyme B expression, reducing the ability of CRC cells to undergo epithelial mesenchymal transition (EMT) and invade Matrigel [74]. ω-3PUFAs also regulate the expression of genes involved in inflammation and colon cancer development through epigenetic modifications [75, 76].

In terms of observational clinical studies, it has been shown that individuals with the highest intake of ω-3PUFAs had a reduced mortality after primary diagnosis of colorectal cancer. Increased ω-3PUFA intake after cancer diagnosis also resulted in reduced mortality [77]. Consumption of animal-derived ω-3PUFAs has also been shown to be associated with a lower risk of primary distal colorectal cancer [78]. In contrast, in patients during adjuvant chemotherapy for completely resected stage III CRC, increased dietary ω-3PUFA intake increases disease-free survival [79]. A meta-analysis by Yu et al. suggests that n-3 fatty acids can significantly help patients after gastrointestinal cancer resection. They reduced inflammation and improved immune function, contributing to faster recovery [80].

There is also an evidence that PUFA-3 intake may be effective both in prevention of the development of Helicobacter pylori infection-dependent gastric cancer, and also may delay the progression of individuals who have already developed this tumour. This is possible by shortening its survival through mechanisms such as inhibition of angiogenesis, proliferation and inflammation. This direction appears to be very promising; however, further detailed clinical studies are needed [81].

**CONCLUSIONS**

In recent decades, inflammatory diseases of digestive system, cancer and obesity affect more and more people. Diet plays an important role in this phenomenon. Modern Western society consumes foods high in omega-6 relative to omega-3 content, which adversely affects health.

There is an evidence that ω-3PUFA supplementation has a positive effect on obesity, IBD and colorectal cancer therapy, but due to the relative scarcity of clinical evidence, our knowledge on this topic needs to be further expanded, as the observation data is certainly promising.

**Ethical approval:** The conducted research is not related to either human or animal use.

**Conflict of interest:** Authors declare no conflict of interest.

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