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Chapter 1

Importance of Fatty Acids in Physiopathology of Human Body

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Additional information is available at the end of the chapter

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Abstract

Fatty acids are important components of the human body, having biological, structural and functional roles. Besides their role as source of energy, they act as main constituents of cellular membranes. In this case, as part of the membrane phospholipids, they assure the fluidity, flexibility, permeability of the membrane and also assure the passive transport through the membrane and are interconnected with other proteins in intra and intercellular way. Among these fatty acids, omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) seem to be the most important, due to their multiple biological roles, such as influencing the inflammatory cascade, reducing the oxidative stress, presenting neuroprotection and cardiovascular protection. Fatty acid levels have been shown to be altered in different diseases, which is why they have been used to identify potential biomarkers for several pathologies, such as polycystic ovary syndrome (PCOS). Consequently, this chapter synthesizes the most important physiological and pathological implications of fatty acids in human body functioning.

Keywords: cell membrane, physiology, pathology, (anti-)inflammatory effect, neuroprotection, cardiovascular disease

1. Introduction

Fatty acids (FAs) are part of the lipid class, widespread in the nature, food and organisms, being an important constituent of the membrane cell. They have important biological functions, structural and functional roles, and they represent an important source of energy. Their metabolism produces a huge quantity of adenosine triphosphate (ATP). The β-oxidation of the fatty acids is a well-known process, mostly used by the heart and the muscular tissue to obtain energy.

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The human body can synthesize many of these fatty acids, except some essential polyunsaturated fatty acids (PUFAs): the linoleic acid (LA) and the α-linolenic acid (ALA). These two are spread especially in different vegetable oils, but their metabolites are found mainly in the fish oil. The linoleic acid is the most abundant fatty acid in nature, and it is the precursor of other omega-6 fatty acids. The omega-3 fatty acids are synthesized from α-linolenic acid. The human body cannot synthesize fatty acids with odd number of carbon atoms chain; however, there were studies in which this type of fatty acids were identified in a low concentration in plasma [1].

Once ingested, short chain PUFAs are converted to long-chain fatty acids. These are critical for mammalian cells in order to perform various biological functions, such as sustaining the structural integrity of cellular membranes and serving as signaling molecules. They are highly enriched in the adipose tissues, for example in the brain, where they participate in the development and maintenance of the central nervous system during both embryonic and adult stages [2].

The fatty acids can be identified and quantified using various analytical methods, but the most widely used technique is the gas chromatography (GC). Its main advantages are selectivity, sensibility and efficiency. One of the disadvantages of this technique is that before the main analysis, a derivatization of fatty acids is necessary to obtain the methyl esters and this way to increase their volatility. Other analytical techniques used for the detection of fatty acids mentioned in the literature were the high performance liquid chromatography (HPLC) or the capillary electrophoresis (CE) [3, 4].

The aim of this chapter was to present some of the alterations in plasma and other biological fluids fatty acid profile in different diseases, some potential biomarkers in each case and to highlight the fatty acids importance in the proper functioning of the human organism.

2. Physiology of fatty acids

Fatty acids are widely spread through the whole human organism, and they can be found under different forms: free circulating fatty acids or esterified, taking form of:

- triacylglycerols (or triglycerides), when esterified with glycerol,
- phospholipids, when esterified with phosphoric acid,
- glycolipids, when combined with glucose or other saccharides,
- sphingolipids, etc.

The great importance of fatty acids resides in the fact that they are main constituents of the human cell. The type of fatty acid, saturated or unsaturated, long-chained or short-chained can influence the physiology of the cell, as it will be described below.

2.1. Fatty acids in the human cell

Every human cell is formed by a membrane, the cytoplasm and the nucleus. The membrane, the barrier which not only protects the cell from the outside world but also which

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has the role in transporting nutrients inside and outside of the cell, is formed of a bilayer of lipids with role in the passive transport and proteins with role in the active transport (**Figure 1**) [5].

This double layer of lipids, which assures the main structure of the cell membrane, is formed of two layers of phospholipids. In this case, the phosphoric acid is esterified with a diacylglycerol (R1, R2), which can contain the same or different fatty acid residues, and another residue (R3) directly connected on phosphoric acid is another type of molecule (**Figure 2**). The phospholipid molecule gets, in this way, an amphiphilic character, which means it is in the same time hydrophilic, due to its phosphoric "head", and hydrophobic, due to the fatty acid "tails". In the cell membrane, the phospholipids are oriented in the bilayer with the hydrophilic head toward the outside of the layer, whereas hydrophobic tails remain on the inside of the bilayer, as seen in **Figure 1**.

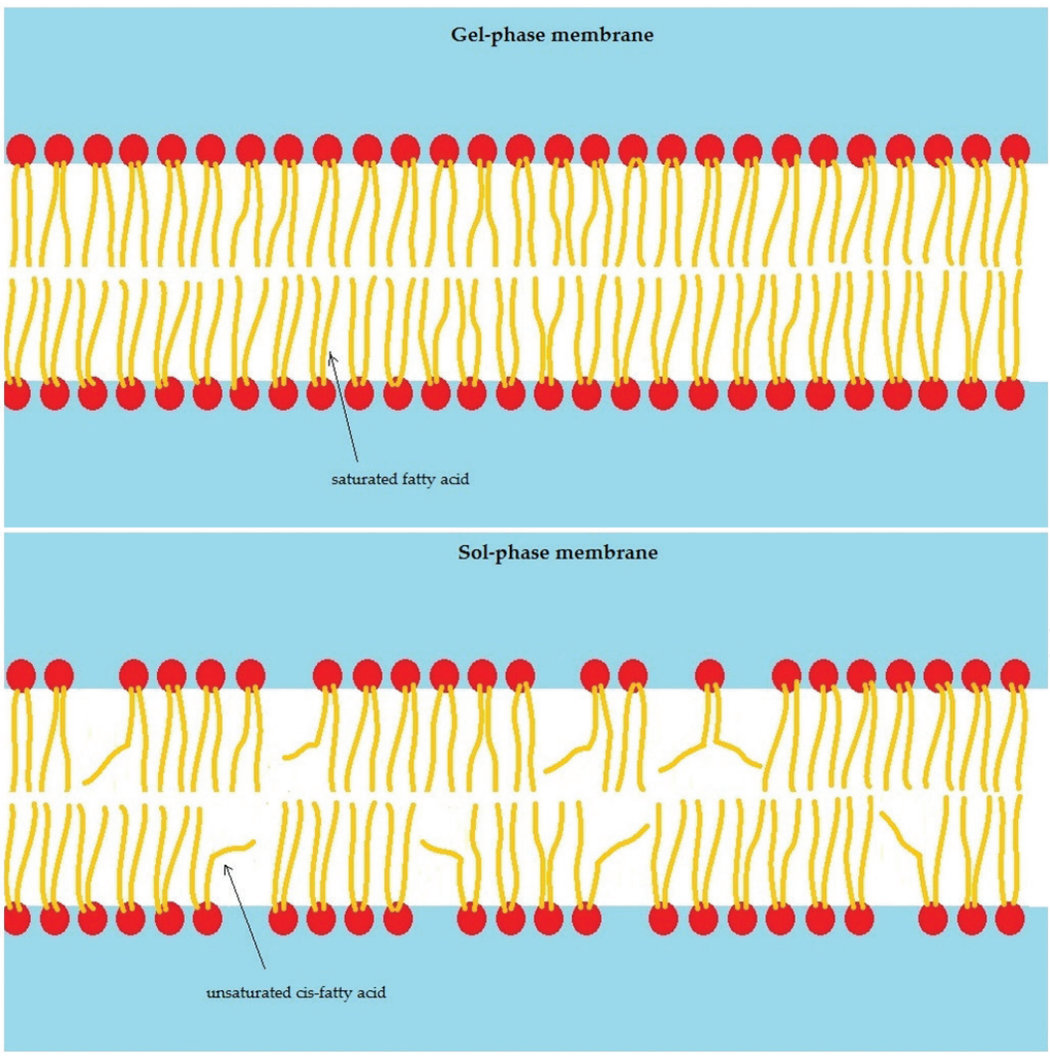


Figure 1. Different fluidity of cell membranes depending on the saturation of fatty acids: saturated fatty acids forming viscous membrane (up), unsaturated *cis* fatty acids forming fluid membrane (down).

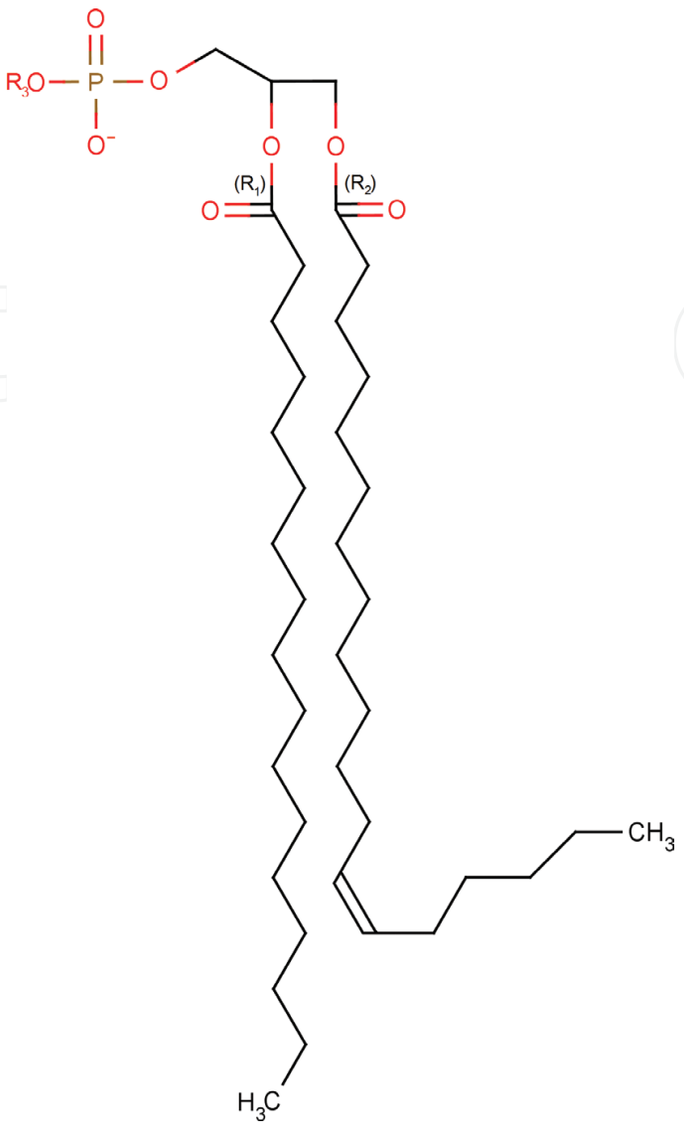


Figure 2. General structure of a phospholipid.

The type of fatty acids found in the structure of the cell membrane can affect its fluidity, its stability and its functions. First, the saturation [6] of fatty acids influences the fluidity of membranes. Thus, if the membrane is composed mostly of saturated fatty acids, which have a straight rigid chain, the phospholipids will form a more rigid bilayer, whereas a membrane formed by many *cis*-unsaturated fatty acids will be more flexible (**Figure 1**). This fact can explain the beneficial effect of polyunsaturated fatty acids on arterial and venous walls, increasing their flexibility and having positive effects in cardiovascular diseases.

One might think that a high content of polyunsaturated fatty acids in cell membranes could expose them to oxidative stress and, consequently, to lipid oxidation and peroxidation [7], but Clinics A [8] has revealed the theory of "triple cell membrane synergy", which states that fatty acids in phospholipids in membranes are surrounded by protective antioxidants. It seems that this hyperfluidity of membranes is obtained in bilayers rich in docosahexaenoic

acid (DHA) [6] and is necessary in cells with high and rapid activity, such as rhodopsin disks or axons. In case of rhodopsin disks, the high fluidity of the membrane (~50% DHA) seems to contribute to the fast transport of rhodopsin on the two sides of the membrane, facilitating the initiation of the visual cascade. In case of axons, keeping the hyperfluidity theory of highly rich DHA membranes, this helps increase their permeability and avoid forming gel-phase islands, which could happen in case of lesser unsaturated fatty acids or even saturated and which would lead to a drastic change of the electrochemical behavior of the axon. In the same time, the DHA-rich membrane assures the differentials in Na^+ (outside of the cell) and K^+ (inside of the cell) necessary for signal transmission.

Moreover, studies have revealed [9] that the docosahexaenoic acid found in the structure of the membrane bilayer can influence the activity of the Na^+-K^+-ATPase pump in the same membrane; the DHA content was significantly correlated with the pump activity in heart and kidney tissues, but not in brain tissues. However, in brain tissues, both DHA concentrations and Na^+-K^+-ATPase were found to be the highest, indicating that DHA content increases in tissues with high energy needs. The authors [10] have mentioned other ionic transport proteins, which are modulated by DHA concentrations, such as voltage-gated K^+-channels, voltage-sensitive-Na^+ channels in myocardial cells or L-type Ca^{2+} channels.

In the same time, membrane protein activity can be affected by external fatty acids released by other cells activity or by exogenous source (diet) [11]. Studies have shown that syntaxin-3 activity is dependent on the presence of omega-6 arachidonic acid. Syntaxin-3, a cell membrane protein responsible for neurite outgrowth, is activated by forming a complex with the synaptosomal-associated protein of 25 kDa (SNAP25). (SNAP25). The formation of this complex has been found to be dependant on the presence of arachidonic acid, at a half-maximal effective concentration of ~100 μM. Other omega-3, such as docosahexaenoic and linoleic acid, omega-6 and linolenic acid have shown the same capacity to activate membrane syntaxin-3. This can explain the specific relevance of omega-3 and omega-6 fatty acids in good functioning of brain activity, neuronal regeneration, neurite outgrowth and their beneficial effects in degenerative neurological diseases. DHA content seems to be connected with its anti-cancer effect, influencing the activity of sphingomyelinase. The activity of protein kinase C (PKC) has been reported to be increased at high levels of DHA in membranes, where DHA is incorporated in complexes with phosphatidylethanolamine and lesser with phosphatidylcholine [10]. Other proteins influenced by DHA presence and/or concentrations reported are phospholipases A2 and C, cytochrome P450SCC or the insulin receptor.

2.2. Omega-3 and omega-6 fatty acids

The omega-3 and omega-6 fatty acids are long-chain polyunsaturated fatty acids with the first double bond located at the third, respectively, the sixth carbon atom related to the methyl end, having a *cis* configuration. The omega-3 and omega-6 PUFA families are essential fatty acids in humans, because they cannot be synthesized *de novo.* The omega-6 fatty acids are the predominant PUFAs in all diets, with the linoleic acid as their representative. The α-linolenic fatty acid is an omega-3 PUFA, which is the precursor of other omega-3 long-chain polyunsaturated fatty acids (LC-PUFAs) [12].

For their metabolism, both omega-3 and omega-6 fatty acids use the same pathway, including the same enzymes. Linoleic acid is converted into arachidonic acid through the steps presented in **Figure 3**. This fatty acid is the most important omega-6 polyunsaturated fatty acid. The arachidonic acid (AA) can be also released from cell membranes through the action of phospholipase A_2 and serves as precursor for the synthesis of the biologically active eicosanoids. These eicosanoids are the prostaglandins (PG), thromboxanes and leukotrienes. There are three types of PG: PG1, PG2 and PG3. The first one has many beneficial effects, it reduces inflammation and helps the body to recover from injury by reducing swelling and redness. PG2 has the exact opposite effect of PG1. This increases inflammation, vasoconstriction and blood clotting. PG3 has a mixture of functions in the body, from which the most important one is represented by the property to reduce inflammation caused by PG2. Dihomo-γ-linolenic acid (DGLA), an intermediate metabolite of the omega-6 pathway, can be converted to either the anti-inflammatory PG1 or into the arachidonic acid, a precursor of PG2. This transformation requires the enzyme Δ5-desaturase, whose activity can be limited. Also, the activity of the Δ6-desaturase can be compromised during inflammatory conditions. Both of these enzyme activities are influenced by diet and environmental factors. In diets high in omega-3 fatty acids, most of the enzyme Δ5-desaturase will be used in the omega-3 pathway, so DGLA will be converted into an anti-inflammatory PG1. Contrariwise, a diet low in omega-3 fatty acids will convert DGLA into AA, and this way the inflammation will increase. A balance of omega-3 and omega-6 fatty acid is therefore essential for a proper health [13].

Competition between the omega-6 and omega-3 fatty acids occurs in prostaglandin formation. Eicosapentaenoic acid (EPA) competes with arachidonic acid for prostaglandin and leukotriene synthesis at the cyclooxygenase and lipoxygenase level. Metabolism of the arachidonic acid by the cyclooxygenase enzyme gives rise to the 2-series prostaglandins and thromboxanes and by the 5-lipooxygenase (LOX) pathway hydroxy, hydroperoxy derivatives and the 4-series of leukotrienes are formed (**Figure 4**) [13].

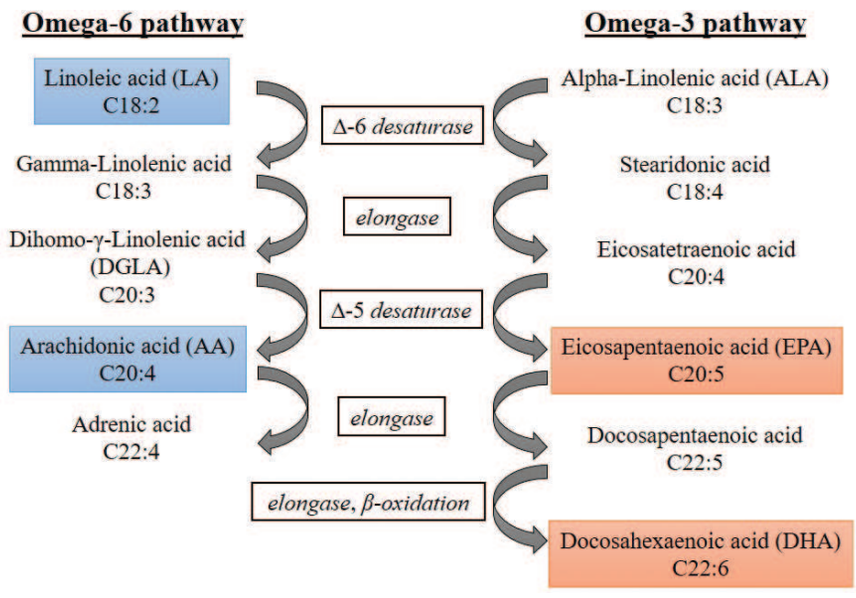


Figure 3. The omega-3 and omega-6 metabolism pathways.

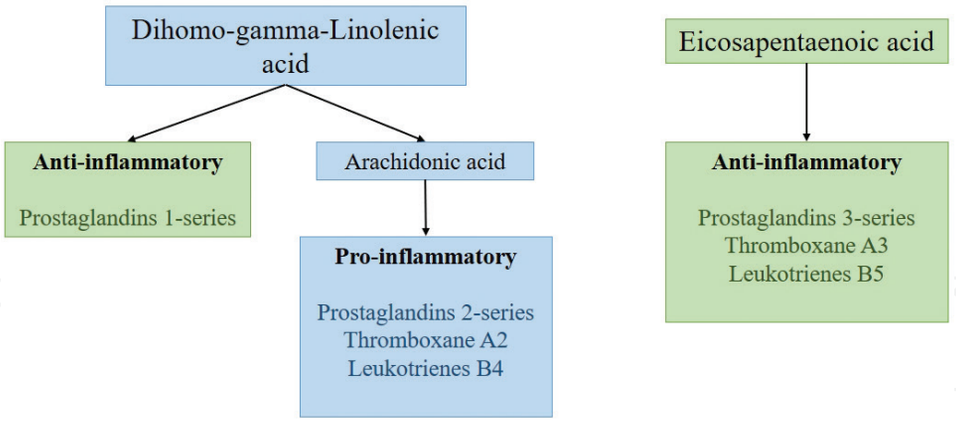


Figure 4. Pro- and anti-inflammatory metabolites of omega-3 and omega-6 fatty acids.

3. Fatty acids with pathological implications

The inflammatory process appears when the human body tries to fight infection and/or to repair damaged tissue. Most of the time this process is protective, but sometimes it can be transformed into chronic inflammation, which can lead to the development or progression of some chronic diseases, including rheumatoid arthritis, coronary vascular disease, cancer and neurological diseases [14]. Fatty acids from diet can influence people's health condition, and they can deteriorate or ameliorate the evolution of some diseases. Scientists try to identify biomarkers for different diseases in order to be able to observe their evolution, to distinguish the ones with similar symptoms and be able to give a precise diagnose. According to Biomarkers Definitions Working Group, 2001 [15], these biomarkers are defined as "Measurable characteristics that reflect biological function or dysfunction, response to a therapeutic measure, or indication of the natural progression of a disease." They are not only useful for disease risk determination but are also extremely useful in establishing a diagnosis. An ideal diagnostic biomarker would reliably reflect *in vivo* pathology with high sensitivity and specificity, while a screening biomarker would combine at least moderate sensitivity with high specificity and low cost.

3.1. Cardiovascular diseases (CVDs)

It became well known over the years that the omega-3 fatty acids have a high impact on health and play an important role in cardiovascular disease prevention. According to the American Heart Association, heart and blood vessel diseases are related to a process called atherosclerosis, which can cause a heart attack or stroke. The role of inflammation in the atherosclerosis process is well known, as well as the fact that omega-3 fatty acids can modify inflammatory cascades favorably, which may be an important factor in their protective role. Their beneficial effects regarding the cardiovascular diseases are mediated by their anti-arrhythmic, lipid lowering, anti-thrombotic and anti-inflammatory properties.

Based on large randomized control trials and *in vitro* molecular experiments, different hypotheses have been proposed for the mechanism of action of these fatty acids regarding the cardiovascular diseases. Several animal studies have demonstrated that omega-3 PUFAs

have beneficial effects in the cardiovascular system, including anti-thrombotic, endothelial relaxation and anti-fibrotic effects [16]. One of the most important, the anti-atherosclerotic effect of the fatty acids, can be explained through their anti-inflammatory effect and their influence on oxidative stress, endothelial dysfunction and homeostasis. Atherosclerosis is characterized not only by inflammation but also by an endothelial dysfunction. This is caused by an epoxide hydrolase that converts the epoxyeicosatrienoic acids (EETs) to dihydroxyeicosatrienoic acids (DHETs). Decreasing this enzyme activity and increasing the EETs/DHETs ratio can have a beneficial effect on the endothelium function [17]. The epoxyeicosatrienoic acids generated from AA induce vasodilatation, stimulate angiogenesis and protect heart from ischemia. CYP450 monooxygenase also converts EPA and DHA to epoxyeicosatetraenoic acids (EpETEs) and epoxydocosapentaenoic acid (EpDPAs), which have similar properties to EETs [16].

Based on clinical trials, it has been observed that omega-3 fatty acids can reduce the hepatic triglyceride synthesis and increase the clearance of circulating ones [17]. According to this, they can have an important role in the management of the type III hyperlipidemia.

Besides these roles, the omega-3 fatty acids have an important anti-arrhythmic effect because they stabilize the partially depolarized ischemic myocytes by shortening the action potential duration and by slowing down the impulse conduction [17]. Due to their length and their increased number of double bonds, they can influence the function of different membrane proteins and can modulate the sodium channel function in cardiomyocytes, leading to antiarrhythmic effect. EPA and DHA also modulate the activity of L-type calcium channels, leading to a reduction in free cytosolic calcium ion, which stabilizes myocyte electrical excitability [16].

However, the best studied effect of the omega-3 and omega-6 fatty acids is the inflammatory one. The anti-inflammatory properties of omega-3 PUFAs have been conventionally attributed to their capability to interact with the main inflammatory signaling pathways and to their suppressive effect on inflammatory cytokine production [18]. The fatty acid metabolites are represented by different types of mediators with both inflammatory and anti-inflammatory properties. There are two types of prostaglandins, one derived from arachidonic acid, with inflammatory, platelet aggregation and vasoconstriction effect, and another one derived from EPA with the exact opposite effect. Besides this, EPA and DHA are the precursors of lipoxins, resolvins and protectins, which also regulate vascular tone and blood pressure [17]. Resolvin E-series are synthesized from EPA through the conversion of 18-hydroxyeicosapentaenoic acid (18-HEPE), and protectins, resolvin D-series and maresins are DHA-derived mediators (**Figure 5**) [16]. An increased level of omega-3 PUFA was associated with a decreased circulating concentration of inflammatory cytokines, such as tumor necrosis factor (TNF), interleukin IL-1β and IL-6.

EPA and DHA downregulate the expression of inflammation-related genes through the nuclear peroxisome proliferator-activated receptor (PPARα/γ) [16]. This nuclear receptor has been linked to *in vivo* lipid metabolism, considering that its activation stimulates β-oxidation and decreases the circulating levels of triglycerides and free FAs, which prevents adipocyte hypertrophy and hyperplasia [19].

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Besides all of these mechanisms, omega-3 fatty acids increase the endothelial nitric oxide production, which result in a vasodilatory response [17]. A summary of all these cardiovascular effects of the omega-3 fatty acids is presented in **Figure 6**.

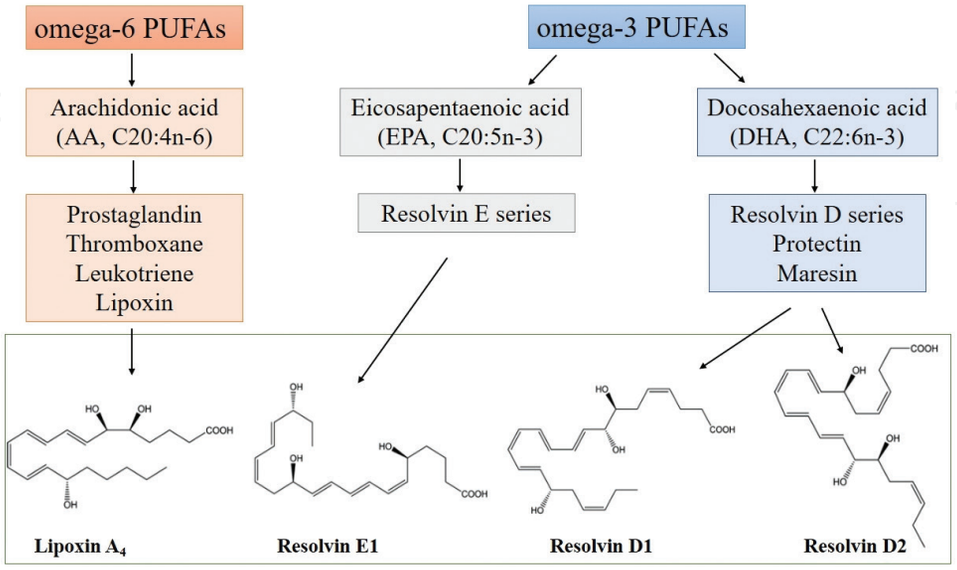


Figure 5. New lipid mediators: resolvins and lipoxins synthesis.

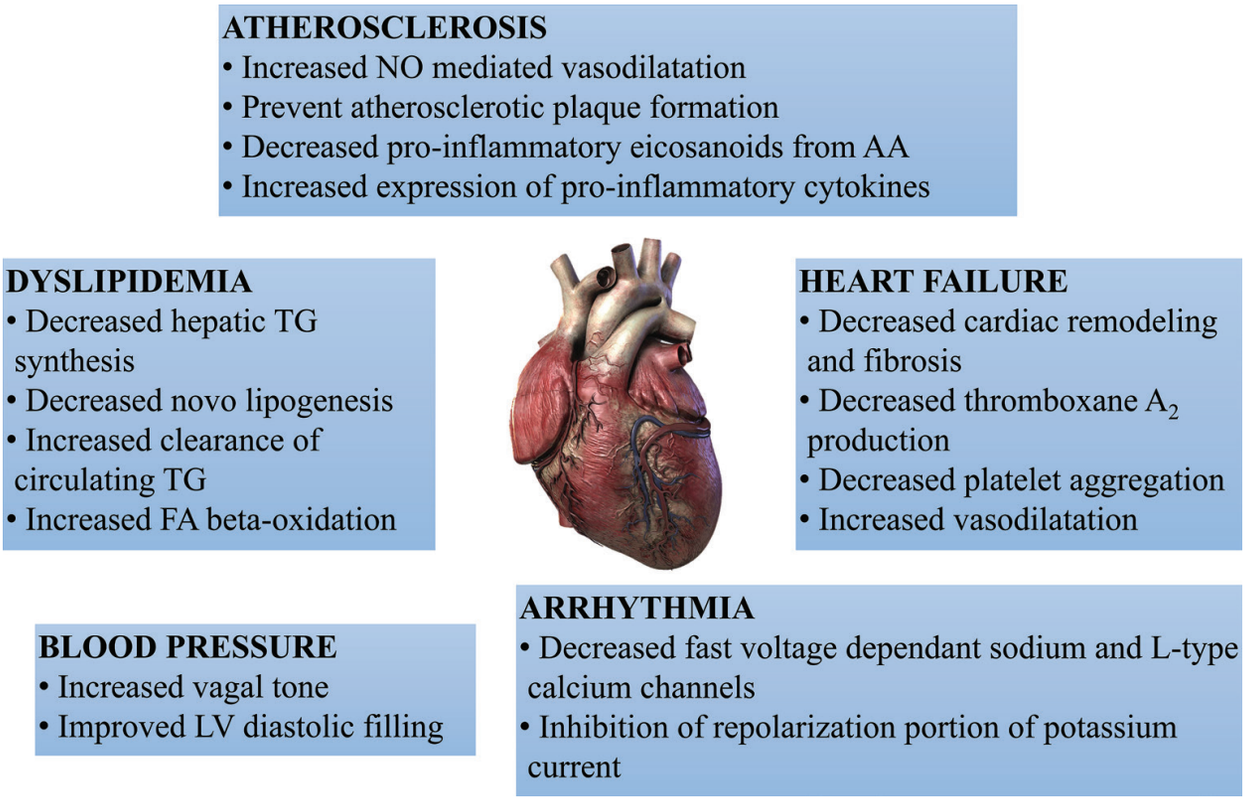


Figure 6. The cardiovascular effects of omega-3 polyunsaturated fatty acids.

Many studies have shown the importance of the omega-3 index. This was developed by Harris and von Schacky and it is defined as the percentage of EPA+DHA content in the red blood cell membranes. An omega-3 index of less than 4% indicates a low cardioprotection. A low omega-3 index is also associated with an increased risk of ventricular fibrillation during acute ischemic phase of myocardial infarction and sudden cardiac death [17], whereas levels higher than 8% confer cardioprotection. Smoking, a major risk factor for the development of the cardiovascular diseases, and higher body weight were associated with lower EPA+DHA levels. Also an inverse association was found between the levels of triglycerides and very low-density lipoprotein (VLDL) and the omega 3-index.

Contrary to the beneficial effects of the omega-3 fatty acids, consuming large amounts of omega-6 FAs increases the plasma concentrations of eicosanoids derived from AA metabolism, specifically prostaglandins, thromboxane, leukotrienes, hydroxylated FAs and lipoxins. These bioactive products have an important inflammatory, thrombosis and atherosclerosis properties and contribute to the development of allergic and inflammatory disorders and excessive cell proliferation [19]. Some studies highlight the importance of omega-6 PUFA/omega-3 PUFA ratio, because a high ratio promotes the pathogenesis of many diseases, including cardiovascular diseases, but not only. It is also associated with inflammatory markers, including C-reactive protein and IL-6. A low omega-6/omega-3 ratio has beneficial effect on patients with asthma and suppresses inflammation in patients with rheumatoid arthritis.

3.2. Rheumatoid arthritis (RA)

Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic inflammation of the joints and progressive joint destruction. The exact mechanism why the body's immune system attacks the joints is still unclear, but many studies have shown that beside the immunologic etiology there are alterations of different metabolic pathways. The plasma metabolic changes can clarify the pathological mechanism [20]. Several studies have shown an association between synovial inflammation and increased free fatty acid concentration in plasma, which demonstrates that the fat metabolism is accelerated in rheumatoid arthritis [21]. Many of these are related to inflammation and might be considered a marker of arthritic inflammation in different stages [20]. One of these fatty acids, stearic acid, was found in higher levels in patients with established rheumatoid arthritis than in patients in early stages [22].

All of these metabolic changes can be evidenced using a GC-MS method. Fatty acids are extracted from different biological samples using an organic solvent or a solid phase extraction. This step is followed by a derivatization process, when the fatty acid methyl esters are obtained. The main analysis of these compounds can be performed using both polar and non-polar capillary phases, a gradient temperature and helium as a carrier gas. The identification and separation of free fatty acids can also be done with a HPLC system, using different mobile phases in isocratic/gradient elution.

The protective effect of docosahexaenoic acid, an omega-3 polyunsaturated fatty acid, is recognized in many types of chronic inflammatory conditions, because this fatty acid can be metabolized into bioactive lipid mediators with anti-inflammatory activities, as described above. A high concentration of omega-3 PUFA is correlated with a reduced number of morning stiffness,

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swollen joints, pain or disease activity. It has also been shown that these fatty acids can reduce the incidence and severity of collagen-induced arthritis. In addition to their anti-inflammatory properties, they inhibit the formation of reactive oxygen species and the AA-mediated induction of tumor necrosis factor receptor type I (TNFRI). They have immune modulatory effect and can affect both T cell function and B cell function [21]. Not only PUFAs but also some monounsaturated fatty acids, such as oleic acid, have a benefic effect, due to their anti-inflammatory properties [20]. RA patients, with an elevated inflammation have a decreased level of all these fatty acids: oleic, palmitic, EPA, DHA acid, compared to healthy controls. Differences were unrelated to age, gender or body mass index (BMI) [22]. Besides their anti-inflammatory activity, omega-3 PUFAs incorporated into phospholipids can result into other lipid mediators (resolvins, protectins) with an increased anti-inflammatory activity and an altered cytokine gene expression [14]. However, the high levels of the omega-6 fatty acids, mainly the arachidonic acid, were positively correlated with synovitis. This happened because AA is the main substrate for the synthesis of the pro-inflammatory mediators, such as cytokines and eicosanoids.

The phosphatidylcholine/lysophosphatidylcholine ratio was lower in serum of RA patients compared to healthy individuals, which can result in higher levels of free fatty acids. Other lipid mediators, such as oxylipins, were also detected in plasma. The most prominent eicosanoid of the LOX pathway found in plasma was 5-hydroxyeicosatetraenoic acid (5-HETE) [21]. Another biomarker in inflammation can be considered the omega-3 index. The inflammatory mediators, C-reactive protein, monocytes and neutrophils, are inversely correlated to DHA, omega-3 index and total omega-3 PUFA [14].

3.3. Neuropsychiatric diseases

Discovering new biomarkers in the field of psychiatry has a huge importance, because they could clarify the etiology of psychiatric problems, confirm the diagnosis of disorders with similar symptoms and predict the course of the disorder and determine how to treat it [15]. Neurodegenerative diseases are caused by several factors, including genetic mutation, membrane damage, mitochondrial dysfunction and a protein or lipid metabolism alteration.

PUFAs are selectively concentrated in synaptic neuronal membranes and regulate vascular and immune functions that affect the central nervous system. Moreover, they have important functions in neurotransmitter signaling. The brain is the most lipid-enriched organ, containing several major lipid classes, including fatty acids. Omega-3 and omega-6 fatty acids constitute 30–35% of total brain fatty acids and have beneficial effects on cognitive function. During brain development, especially in the embryonic stage, polyunsaturated fatty acids are critical for cell proliferation and neuronal differentiation, and their deprivation results in apoptosis. Deregulation of fatty acids is also involved in the pathogenesis of numerous brain disorders, such as neurodegenerative diseases, mental retardation, stroke and trauma [2].

The Alzheimer disease (AD) is a chronic neurodegenerative disease, which usually affects the elderly people and causes dementia. The most common early symptom is difficulty in remembering recent events, but difficulty in speech, disorganized thinking and memory loss is also common. Different morphological modifications of the brain were observed, such as the extracellular amyloid beta (Aβ) depositions and the tau protein abnormalities, the neu-

rofibrillary tangles formation inside the nerve cell bodies. Currently accepted biomarkers of AD include levels of brain chemicals related to amyloid or tau protein and imaging-derived estimates of the size and metabolic activity of specific brain regions. Besides these modifications of the protein metabolism, the lipid metabolism is altered as well, characterized by a decreased level of the omega-3 fatty acids.

Molecular alterations of the fatty acids that persist from preclinical stages through the dementia phase may serve as biomarkers that could aid the early diagnosis of AD. Different stages of AD may have a different gene expression for fatty acid synthesis [2]. In this disease, scientists have revealed alterations in lipid metabolism pathways and in lipid carrier proteins, such as ApoE. Alterations of the lipid metabolism were observed not only in case of patients diagnosed with Alzheimer but also in case of those with other cognitive alterations. In each case, the biggest difference reported between the healthy volunteers and the patients was represented by the level of docosahexaenoic acid. However, other fatty acids presented an altered profile as well. In different studies, a low concentration of palmitic acid (C16:0), oleic acid (C18:1n-9) and some omega-3 fatty acids has been shown, such as α-linolenic acid (C18:3n-3), eicosapentaenoic acid (EPA, C20:5n-3) and docosapentaenoic acid (C22:5n-3) [23].

The monounsaturated fatty acids, mainly the oleic acid, inhibit the production of Aβ and amyloid plaque formation both *in vitro* and *in vivo*. In contrast, arachidonic acid increases Aβ production and the formation of amyloid plaques [2]. Fatty acids contribute to the modulation of the structure and function of biological membranes, including elasticity, membrane organization and ion permeability, and may therefore facilitate brain glucose uptake, neurotransmission and neuronal function.

The docosahexaenoic acid (C22:6) is indispensable for the neuronal myelination, and it is an important precursor for the very long chain fatty acid synthesis (C24:6, C26:6, C28:6, C30:6, C32:6, C34:6), found in the brain. It is also involved in neurogenesis, neurotransmission and protects the brain from the oxidative stress. It has an important role in maintaining the integrity of the basal membrane and as a phospholipid ester maintains the flexibility of the cellular membrane, helping the synaptic transmission, and it can also adjust the speed of the signal transmission. DHA can influence the brain development because it can regulate the gene expression, monoaminergic neurotransmission or protection against apoptotic cell death [24]. During pregnancy, DHA accumulates in human neonatal brain tissue at an accelerated rate during the third trimester in association with rapid changes in cortical structural maturation. A deficit of this fatty acid in the stage of the brain development can lead to the cognitive performance alterations [24].

The polyunsaturated fatty acids, besides their role of maintaining the integrity of the neuronal cell membrane, are involved in the synthesis of eicosapentaenoic acid from which the synthesis of the 3-series prostaglandin and 5-leukotriene begins. EPA has neuroprotective, anti-oxidant and anti-inflammatory properties [24].

This fatty acid inhibits the synthesis of prostaglandins derived from the omega-3 fatty acids, such as PGE2 and PGF2α, which confers an anti-inflammatory property. In case of deficiency of DHA and EPA, the cell permeability modifies and mitochondrial dysfunctions and inflammation appear, and along with the oxidative stress, it plays an important role in the progres-

sion of the disease. DHA and EPA can play a role in alleviating oxidative stress and reducing the risk of neurodegenerative diseases [25]. The novel series of lipid mediators (resolvins, protectins and maresins) have revealed their protective and beneficial effect in neurological diseases, due to their anti-inflammatory and pro-resolving properties.

A simultaneous deficiency of LA and ALA creates serious problems in fatty acid composition of the brain. ALA deficiency alters the course of brain development and perturbed the composition of brain cell membranes, neurons, oligodendrocytes and astrocytes as well as subcellular components such as myelin, nerve endings and mitochondria.

Aging is characterized by a diminution in PPARα expression in various tissues, representing a key target in the prevention of diseases associated with old age. A decrease in the activity of PPARα-regulated genes involved in β-oxidation is accompanied by changes in the composition of FAs in brain. This leads to an increased level of the very long chain saturated fatty acids (SFAs) (C20:0, C22:0, C24:0), monounsaturated fatty acids (MUFAs) (C16:1, C18:1, C20:1, C22:1, C24:1), and decreasing the LC-PUFAs AA and DHA, which are related to the progression of brain aging. It was suggested that PPARα and their endogenous ligands have a role in neuroprotection against oxidative stress, which is key in neurodegenerative diseases, contributing to a normal brain aging. These considerations suggest that endogenous and exogenous PPARα agonists could be useful as a prevention measure for neurodegenerative diseases and ischemic injury, especially in the elderly and/or in patients with high cardiovascular risk [19].

Several other neurological disorders present altered neuronal and plasma fatty acid composition, such as depression, bipolar disorder, schizophrenia and attention deficit hyperactivity disorder.

Depression is accompanied by activation of the inflammatory response system indicated by an increased production of inflammatory cytokines and oxidative biomarker. Cytokine production is accompanied by increased oxidative stress leading to elevated production of reactive oxygen species (ROS) and nitric oxide (NO) or decreased anti-oxidant defense, such as superoxide dismutase (SOD) and glutathione peroxidase. Epidemiological studies also showed that low intake and blood levels of omega-3 PUFAs are associated with an increased risk for being diagnosed with major depressive disorder. Erythrocyte levels of C16:0, C18:0, EPA and the omega-3 index were significantly lower in the case of patients diagnosed with major depression than in the controls, whereas erythrocyte levels of C16:1, C18:3n6, C18:3n3, C18:1t and C18:2t were significantly higher [26]. Different studies suggest that omega-3 fatty acid status influences the development of central serotonin systems. A deficit of the omega-3 fatty acids leads to impaired serotonin release and behavioral signs of depression and aggression. Patients with major depressive disorder present a DHA deficiency compared to healthy controls [27]. The plasma and erythrocyte phospholipid levels of these people showed significant and positive correlation between the ratio of AA/EPA and severity of depression and suicidal behavior.

The patients diagnosed with bipolar disorder presented higher plasma concentrations of all saturated fatty acids than the controls. Lignoceric acid was over 50% higher in the patient group than in the healthy volunteers. In this disorder too, the most important differences between the two groups were represented by the significant decreases in DHA levels and strong increases in levels of EPA and ALA [28].

The presently available data of the literature suggest that the metabolism of PUFAs is altered in patients with schizophrenia, both in the acute and chronic stages of the disease. Altered neuronal membrane structure and metabolism might contribute to some of the symptoms of schizophrenia. A change in membrane lipid composition in neuronal cells can affect neurotransmission and this way can affect the behavior in schizophrenia. Studies showed no difference between the schizophrenia patients and control subjects in the contribution of omega-3 fatty acids to the lipid composition of the phospholipid fraction. However, the values of total omega-6 PUFAs and docosapentaenoic acid are shown to be significantly lower in case of patients with schizophrenia than in case of the control subjects. Membrane lipids seem to fluctuate in different disease phases. This may be related to changes in neuroinflammatory and oxidative processes, which are reported to contribute to disease progression and underlie symptom severity. The healthy group presents stable PUFA levels compared to the patients group. PUFAs are not only important components of neuronal cell membranes but also play an important role in regulation of inflammation through the formation of eicosanoids. Inflammation and oxidative stress may play a role in disease progression through lipid peroxidation and cholesterol oxidation, leading to neuronal cell death [29]. PUFA deficiency will also impair dopaminergic and glutamatergic neurotransmission, which are linked to negative symptoms.

Based on evidence that erythrocyte EPA+DHA composition of total fatty acid lower than 4% increases risk for sudden cardiac death, and evidence that the majority of patients with psychiatric disorders present an omega-3 index lower than 4%, major recurrent psychiatric disorders may increase risk of cardiovascular disease, a principle cause of excess premature mortality in patients with mood and psychotic disorders [27].

3.4. Other pathologies

Inflammation plays a role in the etiology of many types of cancer. It was reported that high concentration of serum long-chain omega-3 fatty acid phospholipids, EPA and DHA, in particular, was associated with the increased risk of high-grade prostate cancer. However, high concentrations of *trans*-fatty acids, which are known to produce inflammation, are associated with a reduced risk of prostate cancer [30]. Other studies have been realized on colorectal cancer tissues from which different fatty acids have been separated. The analysis revealed high concentrations of saturated fatty acids and low levels of monounsaturated fatty acids. Compared to healthy tissues as controls, the malign ones presented a low omega-3/omega-6 PUFA ratio [31]. Likewise, the dysfunction of the lipid metabolism from the hepatocellular carcinoma can lead to an altered plasma lipid profile. The main differences were evidenced in case of C18:2n-6, C20:4n-6, C16:0 and C18:1n-9. These fatty acids can be considered potential biomarkers in case of hepatocellular carcinoma [32].

Obesity is a metabolic disease, and it increases the risk to develop diabetes, non-alcoholic fatty liver disease or other cardiovascular diseases. Compared to healthy volunteers, plasma levels of fatty acids are increased in the obese patients. The biomarker identified in this disease is the increased level of the unsaturated fatty acids, especially the palmitoleic acid (C16:1) and dihomo-gamma-linolenic acid (C20:3) [33]. Studies show that 40% of the people diagnosed with diabetes will develop a kidney or a cardiovascular disease. A high level of omega-3/omega-6 ratio is associated with a low risk to develop a kidney failure. Besides obesity, the

polycystic ovary syndrome (PCOS) can lead to insulin resistance. In this case, two biomarkers were identified: nervonic acid (C24:1) for the presence of PCOS and dihomo-gamma-linolenic acid for insulin resistance [4]. The fatty acid lipolysis in the fatty tissue is increased as well, but the β-oxidation of the fatty acids is decreased. This way the cell permeability and the inflammatory cell infiltration are increased. This may explain why arachidonic acid is considered a biomarker in the plasma of diabetic patients, with or without different stages of nephropathy.

The fatty acid profile is modified in case of an infectious disease, too. In the incipient stage of the dengue fever, a decreased level of C14:0, C16:0, C18:0, C20:4-n6 and C22:6-n3 was observed [4].

Due to the pro-inflammatory and immunoactive properties of the arachidonic acid, a high concentration of this fatty acid and a high level of the AA/EPA ratio are associated with the sickle cell disease and cystic fibrosis. The last one is a genetic disease in which the fatty acid profile is altered. The LA and DHA concentration decreases and increases the concentration of palmitoleic acid and Δ5,8,11-eicosatrienoic acid. In case of cystic fibrosis, the AA concentration increases only at the highest LNA:ALA ratio [4].

The pathobiology of sickle cell disease is initiated by episodic vascular occlusion in which the adherence of circulating blood cells to vascular endothelium is modulated by polyunsaturated fatty acids. Patients diagnosed with this disease have altered red cell and PUFA composition. This is characterized by an increased AA, decreased DHA and EPA levels, and this may play a role in abnormal blood-endothelial cell interactions [34].

Long chain fatty acids are found in a low concentration in plasma, being difficult to identify them. They are synthesized from the short chain fatty acids with the elongase enzyme and are degraded in peroxisome by the β-oxidase enzyme. In the peroxisomal disorders, such as the Zellweger or the adrenoleukodystrophy, the very long chain fatty acids accumulate in the plasma, which leads to the intracellular calcium accumulation and decreases the mitochondrial respiration, which leads to the cellular death of the oligodendrocyte and astrocytes. Important biomarkers in this disease are C26:0, C26:1 and C26:2 [35].

The chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disorder of the airways in which the airways narrow and swell and produce extra mucus. This can make breathing difficult and trigger coughing, wheezing and shortness of breath. Asthma is thought to be caused by a combination of genetic and environmental factors. Once it is installed, the inflammation starts and involves various cell types and mediators. Smoking is one of the major risk factors for the development of COPD, although other risk factors, such as air pollution and genetic factors, exist. In both smokers and COPD patients, a decreased level of omega-3 PUFAs was reported. The C20:5 and the C22:6 were the most significantly decreased, whereas the monounsaturated fatty acid, C16:1, was increased in COPD compared to non-smokers [36]. Many epidemiological studies showed the protective role of DHA in allergic diseases because it suppresses airway eosinophilic inflammation. A new monoglyceride DHA derivative and EPA derivative showed their protective effects on airway inflammation and inflammatory cytokine production. Patients with severe asthma present a selective dysregulation of the 15-lypooxigenase pathway, the reason why a 5-lipoxygenase-dependent metabolite of arachidonic acid, 5-HETE, was similar in patients and healthy subjects [37]. **Table 1** summarizes the biological effects of the most important fatty acids.

Classification	Fatty acid	Biological effect	Diseases
SCFA	Propionic acid	Immunosuppressive effect, improves tissue insulin sensitivity	Prevention of obesity and diabetes type 2
	Butyric acid	Inhibits angiogenesis, antimicrobial effects	Prevention of colorectal cancer, irritable bowel syndrome
MCFA		Thermogenesis, anti-steatosis, weight control	Treating hyperlipidemias, prevention of obesity
LCFA	Oleic acid	Anti-inflammatory effect, inhibit the production of Aβ and amyloid plaque formation	Benefic in rheumatoid arthritis, Alzheimer disease
	α-Linolenic acid (omega-3)	Anti-steatosis, anti-inflammatory	Benefic in Alzheimer disease, CVD prevention, increases prostate cancer risk
	EPA+DHA (omega-3)	Anti-inflammatory, anti-arrhythmic, anti-atherosclerotic	Prevention of obesity, CVDs, beneficial effect in Alzheimer disease, brain development, rheumatoid arthritis, type 2 diabetes
	Arachidonic acid (omega-6)	Inflammatory, platelet aggregation, vasoconstriction, immuno-active properties	Promotes synovitis, Alzheimer disease, diabetes, sickle-cell disease, cystic fibrosis

Table 1. Summary table of biological effects of some FA and their implications in some pathologies.

A significant consumption of omega-3 PUFAs results in a decreased level of arachidonic acid in the membranes of inflammatory cells. This will lead to a decreased level of pro-inflammatory eicosanoids. There is a large amount of literature based on studies investigating the effects of omega-3 PUFAs on inflammation and immune function. The most studies are investigating the fish oil effect on human health. The omega-6/omega-3 fatty acids ratio from modern diets is ranged from 15:1 to 17:1 although it should be 1:1 [8]. The cardioprotective effect of the omega-3 fatty acid was well studied, that is why The American Heart Association recommends 3 g/day EPA+DHA for reducing elevated triglyceride levels [38]. Many studies have been published on the effect of omega-3 PUFAs on brain structure and function. Most of them indicate an increased functional activation in children, although not all of them found any effect of omega-3 fatty acids on cognition [24].

4. Conclusions

In conclusion, this chapter demonstrates the importance of fatty acids in human health, both regarding on the physiology of human body, but also influencing the appearance and/or evolution of different diseases, which are seemingly not related. In this way, especially omega-3 and omega-6 fatty acids become a common point to these pathologies, such as cardiovascular, neurologic, oncologic or endocrinologic diseases, due to their mechanism of action at a cellular level. We have proved the protective effect of DHA and EPA on different types of tissues; however, other types of fatty acids are not to be ignored.

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