Cardiovascular diseases, depression disorders and potential effects of omega-3 fatty acids

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Summary

Cardiovascular disease (CVD) and depressive disorders (DD) are two of the most prevalent health problems in the world. Although CVD and depression have different origin, they share some common pathophysiological characteristics and risk factors, such as the increased production of proinflammatory cytokines, endothelial dysfunction, blood flow abnormalities, decreased glucose metabolism, elevated plasma homocysteine levels, oxidative stress and disorder in vitamin D metabolism. Current findings confirm the common underlying factors for both pathologies, which are related to dramatic dietary changes in the mid-19th century. By changing dietary ratio of omega-6 to omega-3 fatty acids from 1:1 to 15-20:1 some changes in metabolism were induced, such as increased pro-inflammatory mediators and modulations of different signaling pathways following pathophysiological response related to both, cardiovascular diseases and depressive disorders.

Cardiovascular disease (CVD) and depressive disorders (DD) are two of the most prevalent health problems in the world. Ten-fold increase in CVD and depressive disorders in the contrary to two-fold increase in cancer over the last 150 – 180 years in western countries was observed. Although CVD and depression are very different pathologies, they share some common pathophysiological characteristics and risk factors, such as the increased production of pro-inflammatory cytokines, endothelial dysfunction, blood flow abnormalities, decreased glucose metabolism, elevated plasma homocysteine levels and disorder in vitamin D metabolism (Grosso 2014). Several common pathophysiological features underline the importance of environmental factors in mental disorders and CVD. One of the factors that could explain the parallels in these diseases could be related to a dramatic change in dietary habits and intake of polyunsaturated fatty acids (PUFAs, polyunsaturated fatty acids) in favor of saturated fatty acids (FA) and to the increase of the ratio of omega-6 FA to omega -3 FA in the last 150 to 180 years (Simopoulos 2002).

Substantial changes in dietary habits have been accompanied by the increased prevalence of both, CVD and depressive disorders.

The main source of food for our ancestors before the agricultural and industrial revolution in the mid-19th century was the lean meat, fish, green leafy plants, fruits and various berries. Their diet contained only few cereals and saccharides and honey as a sweetener. For this type of diet our genetic material has been furnished. However, especially in the last 150 years, there was a dramatic shift from the food to which the human body was genetically programmed and adapted for millennia. After industrial and agricultural revolution, people have changed their dietary habits, cereals became a central part of the diet, composition of fats was considerably changed, intake of omega-6 fatty acids was increased and the ratio of omega-6 fatty acids to omega-3 fatty acids has been changed from the original 1:1 to 15 - 20:1. Unlike our ancestors, when 90% of the diet consisted of a very wide range of different plants, today the main components of food are cereal grains, in particular wheat, maize and rice. These dietary changes have resulted in the development of several diseases, such as CVD, diabetes mellitus and mental disorders. Several epidemiological and experimental studies have highlighted the potential role of omega-3 fatty acids in the prevention and treatment of CVD (Sinclair 1956, Tavazzi et al. 2008, Oikawa et al. 2009, Di Minno et al., 2010, Delgado-Lista et al. 2012) as well as psychiatric disorders, such as depressive disorders (Lin and Su 2007, Sublette et al. 2011, Lin et al., 2012), attention deficit hyperactivity disease (ADHD) (Gow RV et al. 2015, Patrick and Ames 2015) and schizophrenia (Patrick and Ames 2015, Buol and Altamura 2015).

Fatty acids (FA) are monocarboxylic acids mainly bound in lipids with number of carbon atoms exceeding 10. Fatty acids can be saturated or unsaturated. Unsaturated FA containing unsaturated (double) bonds (polyunsaturated fatty acids, PUFAs) are divided into several groups according to the position of the first double bond from so called “n” end (ω, omega end) of the FA chain (the last carbon from the carboxyl group, - COOH): i) omega-3 FA (e.g. alpha linolenic acid, ALA, C18:3; eicosapentaenoic acid, EPA, C20:5; docosahexaenoic acid, DHA, C22:6), ii) omega-6 FA (e.g. linoleic acid, LA, C18:2; arachidonic acid, AA, C20:4), iii) omega-9 FA (oleic acid C18:1). Essential FAs which the body cannot synthesize, and must be supplied in the diet are listed in figure 1.

Figure 1. Essential fatty acids

Non-essential FAs and other lipids can either enter the body exogenously as a component of our food, or be synthesized endogenously in small amounts in cells. Circulating plasma FAs come mainly from triacylglycerols (TAG) after their hydrolysis by lipases. FA concentration in plasma is the result of two opposing processes: FAs supply from food or their endogenous synthesis and from the use of FAs. FAs are used for energy production, incorporation into cell membranes and storage.

Essential FAs obtained from dietary sources of triacylglycerols include:

– LA (omega-6 FA) is present mostly in vegetable oils such as sunflower, canola, hemp, soybean and corn oil, or borage oil and evening primrose, or safflower oil. Less LA is in the flax seed oil. Omega-6 FA is present also in tofu, almonds, walnuts, blackcurrant seeds. In addition to the essential LA, also AA, belongs to the omega-6 FA, which in the human body may be synthesized in tiny amounts from LA by the elongation.

– ALA (omega-3 fatty acid) mainly found in fatty fish such as salmon, tuna, herring, mackerel, anchovies or sardines, but also in the seeds of flax, hemp and the walnuts and in certain vegetables such as kale, spinach, salads. Small amount of ALA can get in the body by consumed chicken and beef. The most important omega-3 fatty acids include EPA, and the most unsaturated FA DHA, which in the body may also be synthesized in tiny amounts from ALA with the same desaturation and elongation enzymes as the AA (Figure 2).

Figure 2. Polyunsaturated fatty acids synthesis from linoleic acid and linolenic acid

In human organism the primary site of synthesis of AA and DHA from LA and ALA required for the brain, is the liver. The synthesis is carried out in the endoplasmic reticulum and is finalized in the peroxisomes of cells. However, in contrast to other mammals, production of DHA from ALA is very slow in human and represents only about 0.5% of the total ALA obtained from food (1 to 1.5 g /day). Synthesis of DHA requires the same desaturases as the synthesis of AA, which are in constant mutual competitions (Salem et al. 1999).

Polyunsaturated fatty acids are transferred from the food to the liver, where AA and DHA are

synthesized from the LA and ALA, and are stored in very low density lipoproteins (VLDL) in the form of triacylglycerols (TAG). From TAG they are released by lipases. Circulating fatty acids AA and DHA are transported by blood bound to albumin or to glycerophospholipids of lipoproteins. They cross the blood-brain barrier (BBB) of nerve cells by passive diffusion, using various protein transporters and receptors (Figure 3).

Figure 3. Fatty acid metabolism

Brain has a different lipid profile than blood. Also distribution of FA in brain is different from other organs and blood. The brain is relatively pure in linoleic and alpha-linolenic acid but it contains more saturated 18-carbon acids and less 16-carbon acids, compared to other tissues. Of the omega-3 fatty acids, DHA is mostly present in the gray matter in the phosphatidylethanolamine and phosphatidylserine (less in phosphatidylcholine) and sparsely in myelin. However, the EPA is present only in trace.

DHA can be synthesized also in the brain, but the speed of its synthesis compared to the liver is very low. Incorporation of DHA/EPA into glycerophospholipids of the cell membrane competes with the incorporation of AA. DHA in cell membranes of the brain affects many properties of the membrane such as the thickness of bi-layer, the free volume of the acyl chains, phase transition temperature, the lateral separation of membrane lipids in the DHA-rich/cholesterol-poor, and vice versa DHA-poor/cholesterol-rich regions and the formation of lipid microdomains (rafts) responsible for modulation and integration of signal transduction (Farooqui et al. 2007, Farooqui 2009, Ma et al. 2004). DHA in the membrane of nerve cells affects its fluidity, thereby affecting the activity of integral membrane proteins, ion channels and neurotransmitter receptors.

However, higher doses of omega-3 FA can exhibit undesirable side effects including increased risk of bleeding, e.g. in the gastrointestinal tract or in the brain (stroke). Gastrointestinal discomfort may include loose stools, diarrhea, nausea, vomiting and loss of appetite. Some symptoms are removed when the FA are consumed with the food. Patients with the planned operation are advised to avoid consumption of polyunsaturated FA 3-7 days before surgery. Chronic administration of FA can cause a deficiency of vitamin E, so some clinicians recommend the additional administration of vitamin E, especially at higher doses of polyunsaturated FA. However, the observed side effects are usually seen in adults, therefore

profile of potential side effects in children can be different from that in adults (Gow and Hibbeln 2014).

Cardiovascular disease (CVD)/Coronary heart diseases including heart attack stroke and heart failure is the leading cause of death and hospitalisation in the world. It is considered the most significant health problem worldwide (Joyn et al. 2003). CVD causes more than half of all deaths across the European Region (WHO, 2007). Cardiovascular disease causes more deaths among Europeans than any other diseases, and in many countries still causes more than twice as many deaths as cancer (Nichols et al. 2014).

The major cause of CVD is atherosclerosis. It is a chronic inflammatory disorder that is developed slowly over many years. The main risk factors of atherosclerosis can be divided into few groups: (1) non modifiable (age, ethnicity, gender, genetics), (2) modifiable by lifestyle (diet, obesity which initiates metabolic syndrome and insulin resistance, smoking leading to the reduction of glutathione peroxidase activity, physical inactivity), (3) modifiable by drugs (dyslipidemia with high level of low density lipoproteins (LDL), hypertension with increased production of angiotensin II), (4) non-traditional risk factors (lipoprotein A, homocysteine, infections, systemic lupus erythematosus).

These risk factors, namely dyslipidemia, hypertension and smoking unite other mechanisms including oxidation and inflammatory processes in the artery wall resulting in rise of characteristic fatty-fibrous lesions. The opinion on the role of oxidative stress in human atherogenesis is still unclear, because clinical trials using antioxidants showed predominantly negative results (Scott 2004). However, in the large prospective study the benefits of traditional mediterranean diet with fish and olives showed reduced oxidative stress suggesting that the problem is more complex and diverse diet provides a mixture of necessary antioxidants in comparison to single one (Trichopoulou et al. 2003).

Inflammation represented by its general marker, C-reactive protein (CRP), is one of central processes in atherogenesis. CRP is produced by the liver in response to pro-inflammatory cytokines such IL-6. It binds oxidised LDL and is present in atherogenic lesions where it may act as a chemoattractant and be involved in the expression of adhesion molecules (Mosca 2002).

Inflammatory mechanisms couple dyslipidemia to atherogenesis. Leukocyte recruitment and expression of pro-inflammatory cytokines characterize early state of

atherogenesis. Inflammatory pathways promote thrombosis, a late and serious complication of atherosclerosis resulting in myocardial infarction and strokes. The recognition of the role of inflammation in atherosclerosis, identification of triggers for inflammation allows to understand the clinical benefits of lipid-lowering therapies and possible new therapeutic targets and approaches. Usually drugs used to treat atherosclerosis like aspirin, statins, peroxisome proliferator-activated receptors alpha agonists, angiotensin II signalling inhibitors, exhibit anti-inflammatory properties and calcium channel blockers (Libby 2002).

The first information about the relation between essential fatty acids and cardiovascular diseases including atherosclerosis was published by Sinclar (1956) after his observations from his first visit of Eskimos in Greenland in 1944. He observed that traditional diet of Inuit population is rich in seal and fish with high contents of omega-3 fatty acids exhibiting antithrombotic effect, which could be the reason for the rare occurence of ischemic heart disease in Greenland Eskimos (Puri 2008). Mizushima et al. (1997) reported results from Japanese epidemiological studies which confirmed a dose-response relationship between the frequency of weekly fish consumption and reduced CVD risk factors (e.g. obesity, hypertension, glycohemoglobin, ST-T segment change on the electrocardiograms) and reduced incidence of cerebro-thrombic diseases.

Over the past 20 years, there has been a marked increase in the scientific investigation and public interest in omega-3 and omega-6 FA and their impact on personal health. Several studies have shown an inverse association between fish consumption and risk of coronary heart disease including sudden cardiac death, like JELIS study (Oikawa et al. 2009), DART study included men recovering from acute myocardial infartion (Burr et al. 2005) or GISSI preventive study with survivors of myocardial infarction (Tavazzi et al. 2008). Also recent reviews have reported beneficial effects of omega-3 FA in preventing cardiovascular and coronary events and cardiac death (Delgado-Lista et al. 2012) and especially in triacylglycerol level decreasing activity (Di Minno et al. 2010) and increasing the clearance of plasma triacylglycerols (Harris et al. 2008). However, some studies have not found any relation between fish consumption or omega-3 FA supplementation and mortality among men with angina (DART-2 trial) (Burr et al. 2003). Omega-3 FA in ten randomized controlled trials did not reduce the secondary risk of sudden cardiac death in patients with CVD (Chen et al. 2011).

These discrepancies can be caused by different design of trials, heterogeneity of subjects included into study according to the primary prevention category or group with high risk for CVD, time of duration, different doses of supplemented omega-3 FA and also different DHA and EPA ratio in the diet (Nestel et al. 2015).

It is supposed that omega-3 FA can be cardioprotective due to multiple mechanisms (Jain et al. 2015):

The benefits of fish oils were originally thought to be due to their antithrombotic effects, but results indicated antiarrhythmic effect as a predominant effect (Din et al. 2004, Rizos and Elisaf 2013).

Effects of omega-3 FA:

1. Antiarrhythmic effect of omega-3 FA – through stabilization of electrical activity of cardiac myocytes by sarcolemmal ion (sodium, potassium and calcium) channel inhibitions resulting in a prolonged relative refractory period. Moreover, omega-3 FA alter the membrane fluidity and thus influencing the ion transport. However, the protection of atrial fibrillation is limited to patients with structural changes of the heart such as heart failure but not with lone atrial fibrillation (Sakabe et al. 2007). Also post-operative atrial fibrillation was not considerably influenced (Mozaffarian et al. 2012).
2. Antithrombic effect was first determined for EPA – it reduces platelet adhesion and reactivity leading to increased bleeding time and namely, it inhibits the synthesis of thromboxane A2, which causes platelet aggregation and vasoconstriction (Connor et al. 1997).
3. Antiinflammatory effect – omega-3 FA are in competition with arachidonic acid, a precursor for the synthesis of pro-inflammatory eicosanoids (Rees et al. 2006). On the other hand, EPA is the substrate for synthesis of anti-atherogenic eicosanoids (Calder, 2009).
4. Inhibition of atherosclerotic plague formation by EPA and DHA – through the reduction of macrophages in atherosclerotic plaque (Plutzky 1999) and reduction of total volume of the atherosclerotic plaque (Thies et al. 2003) and decreasing of platelet-derived growth factor production, a key chemoattractant and mitogen for smooth muscle cells and macrophages.

5. Endothelial function influenced by EPA – through increasing the bioavailability of nitric oxide after the inhibition of superoxide production by neutrophils resulting in increased vasodilatory effect. However, no effects of omega-3 FA on endothelial vasomotor function, tissue plasminogen activator (t-PA) or cluster of differentiation 40 (CD40) and its ligand CD40L was observed in patients with a previous myocardial infarction (Din et al. 2013).
6. Antiatherogenic effect of omega-3 FA on lipid risk factors – high EPA/DHA ratio contributed to a greater decreasing tendency in triacylglycerol levels through the inhibition of their synthesis in liver, however, no marked changes in total cholesterol was recorded in diabetic patients (Chen et al. 2015). In normolipidemic or borderline hyperlipidemic individuals the reduction in circulating triacylglycerols (9-26%) was demonstrated in trials where ≥ 4 g/day of omega-3 FA from food were consumed, while a 4-51% reduction was found in trials where 1-5 g/day of EPA and/or DHA was consumed in supplements. In studies directly comparing EPA and DHA, DHA caused reduction of triacylglycerols more effectively than EPA (-22.4% vs. -15.6%) and elevation of HDL cholesterol (+7.3% vs. 1.4% for EPA). However, also elevation of LDL cholesterol after DHA-containing but not EPA-containing supplements or therapies were observed (Leslie et al. 2015). Omega-3 FA can also markedly reduce atherogenic postprandial lipemia (Harris 2008).
7. Blood flow abnormalities can be modulated by omega-3 FA – omega-3 FA increased forearm blood flow in people with chronic heart failure or in smokers (Din et al. 2013). Fish oil appeared to have more significant effects in younger men, compared to older men. More information is needed in this research area.

Fourty-two years after the publication of Hugh Sinclair‘s research on the essential fatty acids and atherosclerosis in Lancet, another paper in Lancet was published by Joseph Hibbeln (Hibbeln 1998), who in his epidemiological study found a significant negative association between the annual prevalence of major depression and apparent fish consumption (Puri 2008). Several studies have reported reduced level of omega-3 FA in erythrocyte membranes (Edwards et al. 1998) in patients with depression compared to healthy control. Seasonal variation in polyunsaturated fatty acids, particularly EPA was related to a seasonal variation in violent suicide and serotonergic markers of violent

suicide (De Vriese et al. 2004). The first therapeutical use of EPA for the treatment of depression was published by Puri et al. (2001).

Depressive disorders (DD)

The increased incidence of DD in people of western countries has been associated with drastic changes in dietary habits over the century, in which the consumption of omega-3 fatty acids in the form of fish, grain and vegetables has been replaced by the omega-6 FA from cereal oils. The ratio of omega-3 FA to omega-6 FA in the diet has shifted from 1:1 to 1:15 and this switch has coincided with a strong rise in the rates of depression in recent decades. From this follows the hypothesis that omega-3 FA supplementation could be one approach for treating depression and other mood disorders (Caballero-Martínez 2014, Lopresti et al. 2015).

Epidemiological cross-sectional and prospective cohort studies of efficacy of omega-3 FA consumption against depression showed conflicting results (Grosso et al. 2014). No association between the dietary intake of omega-3 FA and depressed mood, major depressive episodes, or suicides were observed in men in Finland (Hakkarainen et al. 2004), Australia (Jacka et al. 2004) and Greece (Kyrozis et al. 2009). On the other hand, potential protective effect of fish consumption rather than omega-3 FA supplementation was found in Fishermen study (Suominen-Taipale et al. 2010). In Danish women during 1 year postpartum a negative association between fish consumption, but not omega-3 FA intake, and postpartum depression was observed (Strøm et al. 2009). In two cohort studies, French study SUVLMAX and SUN study, individuals consuming fatty fish or omega-3 FA higher than 0.1% of energy intake during 2 years had a significantly lower risk for any depressive episode (Astorg et al. 2008, Sanchez-Villegas et al. 2007).

Similarly, also experimental studies have reported some controversial outputs following from several meta-analyses. Despite the reported general positive effects of omega-3 FA intake on improvement of depressive symptoms (Freeman et al. 2006, Lin and Su 2007), some other systemic reviews presented no effect of omega-3 FA on depressive symptoms (Appleton et al. 2006, Rogers et al. 2008).

This discrepancy between results from different studies can be attributed to significant heterogeneity among studies including different protocol and design of the study, duration of supplementation, doses of omega-3 FA, homogeneity of patients (the pathophysiology of

major depression can be different than comorbid depression). For example, our results indicate that patients with depressive episode (according to International Classification of Diseases, ICD-10, F32) are more sensitive to omega-3 FA treatment compared to mixed anxiety and depressive disorder (F41.2) (Trebatická et al. 2016). Also a source of omega-3 FA, their form of application (diet, emulsion, capsules) or especially EPA/DHA ratio can influence final results. Results from recent meta-analyses suggest that EPA rather than DHA had positive effects on depressive symptoms as adjuvant therapy compared to mono-therapy (Grosso et al. 2014). Supplements containing minimally 60% of EPA of total omega-3 FA at dose 200-2200 mg/day of EPA were effective (Sublette et al. 2011). More unrecognized situation is in antidepressant effect of omega-3 FA in children and adolescents (Lopresti 2015). Only two reviewed studies (Nemets et al. 2006, McNamara et al. 2014) evaluated an impact of omega-3 FA on depressive symptoms. Also our results (Trebatická et al. 2016) suggest a significant effect of daily doses of fish oil emulsion providing 2.4 g of total omega-3 FA (1g EPA and 0.750 g DHA, EPA:DHA ratio = 1.33:1) on symptoms determined with CDI score. More sensitive were patients with depressive episodes compared to mixed anxiety and depression.

Hypothesized mechanism of omega-3 FA action in brain function (Liu et al. 2015):

1. Omega-3 FA and signaling in brain – animal studies indicate that omega-3 FA influenced dopaminergic system. For example, in rats fed with omega-3 FA deficient diets lower levels of dopamine, D2 receptors, D2 receptor mRNA and dopaminergic presynaptic vesicles and increased breakdown of dopamine in the prefrontal cortex (Zimmer et al. 1998, 2000) and decreased *tyrosine hydroxylase*, the rate limiting enzyme in dopamine synthesis (Kuperstein et al. 2008) were observed. Conversely, high-omega-3 FA diet exhibits opposite relations involving decreasing *monoamine oxidase B* activity in prefrontal cortex (Chalon et al. 1998). Omega-3 FA can interact with the serotonine (5-hydroxytryptamin; 5-HT). Rats with low level of DHA had lower level of 5-HT and its turnover in frontal cortex and higher density of hippocampal 5-HT_{2A} receptors (Levant et al. 2008). Conversely, in adult male mice under chronic mild stress increased 5-HT level was recorded after omega-3 FA supplementation (Vancassel et al. 2008).

Also some other signaling pathways can be modulated by omega-3 FA, like phosphoinositide pathway through modulation of *phospholipase C* and *protein kinase C* or *calmodulin-dependent protein kinase* involved in Ca^{2+} dependent release of neurotransmitters from synaptic vesicles and *Ca^{2+}-ATPase* in neuronal membranes, which is inhibited by DHA and EPA (Kearns and Haag 2002).

In the recent years the role of increased activity of glutamate receptor and N-methyl-D-aspartate (NMDA) receptor agonism was studied in relation to functional and structural plasticity in the adult brain. An increased activity of glutamatergic system and NMDA receptor agonism is associated with depressed mood (Latour et al. 2013).

2. Omega-3 FA and neuroinflammation – polyunsaturated fatty acids during their catabolism are substrates for few enzymes when different eicosanoids and docosanoids are formed (Figure 7). Arachidonic acid (AA) is released from phospholipids through the action of *phospholipase A2* and than is metabolised by *cyclooxygenase* (COX), *lipoxygenase* (LOX) or *cytochrome P450*. COXs form prostaglandins (PG) and thromboxanes (TBx), LOXs form leukotriens (LT) and *cytochrom P450s* form hydroxyeicosatetraenoic and epoxyeicosatrienoic acids. DHA and EPA formed from alpha-linolenic acid (ALA) are in competition with AA formed from linoleic acid (LA) and their incorporation in cell membrane decreases AA contents and by this way availability of substrate for synthesis of pro-inflammatory eicosanoids, like LTB4, TBx4. On the other hand, anti-inflammatory eicosanoids, like PGF_3 and PGF_{3a} are formed from EPA (Figure 8).

   In depressive patients increased production (during an acute phase response) of pro-inflammatory cytokines such as IL-1 beta, IL-6, IL-12, THF-alpha was observed (Mamalakis et al. 2004, Wichers and Maes 2002). Administration of omega-3 FA to healthy human caused decreased production of tumor necrosis factor (TNF) alpha, IL-1 beta and IL-6, but not in all studies (Dowlati et al. 2010). However, the question is as to whether increased level of omega-3 FA in plasma is related to reduce inflammatory processes in the brain? In recent paper by Calder (2013) a reduction of expression of TNF alpha, IL-6, *NO synthase* and *COX*-2 and upregulation of *heme oxygenase-1* in BV-2 microglia was published. However, some other results indicate that these associations are dose- and time of FA intake-dependent (Lu et al. 2010).

3. Omega-3 FA and neuroprotection – in the contrast to pro-inflammatory eicosanoids derived from omega-6 FA, docosanoids derived from unesterified DHA exhibit stereospecific anti-inflammatory effects also in brain. The three known classes formed from controlled oxidative break-down of DHA or EPA with lipoxygenases within the membrane are resolvins, docosatrienes and protectins (Farooqui et al. 2007, Serhan 2005). Resolvins are divided into two groups, D-series and E-series, depending on the FA they are derived from: either from DHA or EPA, respectively (Orr et al. 2013). Resolvin E1 has been reported to reduce inflammation by suppressing the activation of transcription factor NFκB (Faooqui et al. 2007). Neuroprotectins are able positively affect neuronal survival through altering of pro- or anti-apoptic gene expression (Liu et al. 2015) and resolvins protect the brain from ischemia (Marchesselli et al. 2003). DHA depletion has been shown to result in decreased brain-derived neutrophic factor in rodents and increase of neuronal hippocampal cell death through apoptosis (Akbar et al. 2005).

4. Omega-3 FA in regulation of brain energy – DHA has been also identified as an important regulator of brain energy metabolism (Liu et al. 2015) having effects on both glucose uptake and on the density of glucose transporter-1 in endothelial cell culture and in cerebral cortex from rat brain (Pifferi et al. 2007). Neuroimaging in humans with positron emission tomography has found correlations between plasma fatty acid levels and cerebral metabolic rates for glucose in specific brain regions (Sublette et al. 2009).

5. Hypoperfusion in the limbic system and prefrontal cortex in depressed patients was reported using a pixel-by-pixel basis photon emission computed tomography (SPECT) method (Ito et al. 1996). Using single SPECT method imaging in suicide patients reduction of regional cerebral blood flow was detected in the medial prefrontal cortex (Willeumier et al. 2011). The benefit of omega-3 FA could be attributed also to alteration in blood flow to the brain (Stahl et al. 2008).

Two-way relationship between depression and cardiovascular disease

Several epidemiological, retrospective or review studies have suggested an association between mood state (depression) and cardiovascular diseases (Joynt et al. 2004, Mosovich et al. 2008, Calder and Yaqoop 2009, Hare et al. 2014). CVD and depression are currently the two most common causes of disability in high-income countries. Although manifestation of

these two diseases is different, their relation has bi-directional character. Their prevalence is similar and is greater than average in other medical conditions such as cancer, erectile dysfunction or cerebrovascular diseases (Grippo and Johnson 2002). CVD is the leading cause of death and disability in developed world. Depression is a leading cause of disability worldwide and major determinant of patient adherence to appropriate medical and life-style strategies (Hare et al. 2014).

Depression has been cited as a significant risk factor for recurrent cardiac events and can heighten its severity in patients with established cardiovascular disease. 20-50% of patients who die from myocardial infarction are thought to be significantly depressed prior to the infarction (Grippo and Johnson 2002).

On the other hand, CVD may induce depression. Several studies have found increased rates of depression following a stroke event. The most common form of depression experienced after acute coronary event is an "adjustment" disorder with depressed mood when marked reduction in depression of cardiac patients over time has been seen. However, in patients after the stroke 27% had major depression and 14-18% minor depression (Hare et al. 2014). Several previous papers suggest that depression can influence cardiovascular function, and vice versa cardiovascular diseases also influence affective states. The review of pathophysiological characteristics of CVD and depression is given in Figure 4.

CVD and depression might share a common underlying cause, like neurohormonal activation, rhythm disturbance, inflammation and hypercoagulability, which may initiate both pathological conditions (Figure 4) (Joynt et al. 2004). A number of factors increase an individual's risk for CVD, including smoking, hypertension, diabetes, dyslipidemia, metabolic syndrome, stress or obesity and also for depression including presence of previous depression, depression in family history, difficult life events, substance use disorder, chronic somatic disorder, no relationships, no family, poor social life, loss of mother before 11 years of age, divorce, being single, widow/er, lower socioeconomic status.

Figure 4. Pathophysiological characteristics of cardiovascular diseases and depression disorders

Also some „novel“ risk factors underlying the mutual association between CVD and psychiatric disorders, such as oxidative stress, homocystein or vitamin D have been indentified (Figure 4).

Oxidative stress (more precisely referred to as *redox stress*) as a disturbance in the pro-oxidant/antioxidant balance in favour of the former, is leading to potential damage (Ďuračková 2014). Oxidative stress at low level exhibits some biomodulating activities in signaling and functioning of cells relevant to pathogenesis of CVD and psychiatric disorders including the effect on cell proliferation, apoptosis, survival or generally on the cell fate (Ďuračková 2010). However, at high level oxidative stress can be deleterious and may be intrinsically involved in the shared disposition for both CVD and psychiatric disorder. It is supposed that through FA peroxidation oxidative stress could be a mediator in the brain (modest antioxidant defence and highly oxidizable substrate – lipids) and cardiovascular system (atherosclerosis, diabetes mellitus or insuline resistance development, increased mitochondrial production of ROS, inverse correlations between antioxidant enzymes and CVD). Oxidative stress mediated structural and functional effects on FA metabolism including FA peroxidation products may underlie the clinical overlap between CVD risk factors and psychiatric disorders through decreasing of long-chain PUFAs, omega-3/omega-6 FA ratio, changing activities of desaturases and increasing pro-inflammatory eicosanoids (Assies. et al. 2014).

However, the final effect of oxidative stress on fate of cells, organs or organism is dependent not only on pro-oxidant/antioxidant balance, but also on the type of oxidants, type of missing antioxidants, and on the duration and the intensity of oxidative stress (Ďuračková 2010). For example, oxidative stress may be an early causative factor in CVD pathology rather than a late consequence. McCarthy (2014) discussed results of Assies et al. (2014) and concluded that authors explained how oxidative stress may impact simultaneously upon cardiac, metabolic and mental health. They showed biochemical changes following oxidative stress as protective responses to cellular damage and not necessary harmful events. These considerations may explain the failure of supplementation of omega-3 FA in clinical practice (McCarthy 2014).

Oxidative stress is related also to C1 cycle, where aminoacid homocysteine (HCy) is a key metabolite. **Hyperhomocysteinemia** over 10 μmol/L is considered a significant risk

factor for CVD as well as for affective disorders. HCy level was not changed after medication of antidepressant fluoxetine. However, lowering HCy level in patients supplemented with folic acid resulted in antidepressive actions more efficient than those seen in patients treated with fluoxetine alone (Coppen and Bailey 2000, Severus et al. 2001).

At the physiological conditions, HCy reacts with endothelial NO, endothelium-derived relaxing factor (EDRF) to form S-nitrosohomocysteine with vasodilatory and antiplatelet effects. HCy is metabolised by two different pathways. One is re-methylation of HCy to methionine with N5-methyltetrahydrofolate and vitamin B12 as cofactors. Subsequent activation of methionine by adenosine triphosphate to form S-adenosylmethionine is required. The second pathway is transsulfuration reaction in which cysteine is formed with vitamin B6 as a cofactor (Figure 5). From methionine is formed S-adenosylmethionine, a basic methylation agent in the metabolism for methylation of proteins. During proteolysis from methylated rest of arginine unit asymmetric dimethylarginine (ADMA) can be formed. ADMA can competitively inhibit endothelial eNOS and thus inhibit NO production leading to endothelium dysfunction (Dayal and Lentz 2005). Similarly, neuronal nNOS can be inhibited by ADMA in cerebrospinal fluids (Pluta 2008). In addition to simple proteins, also histones in deoxyribonucleoproteins (during histones methylation) and fatty acids in lipids (during elongation of PUFA) can be methylated by ADMA. By this way, epigenetic regulation of omega-3 FA synthesis can be performed (Figure 5). On the other hand, during transsulfuration pathway, HCy can be converted to cysteine, a basic precursor for synthesis of important endogenous antioxidant glutathione.

However, at high level HCy can be converted into HCy-thiolactone (Jakubowski 2008). Through autooxidation of HCy H_2O_2 and superoxide can be formed and contribute to endothelial toxicity (Stamler et al. 1993). Moreover, HCy can inhibit *glutathione peroxidase*, an antioxidant enzyme degrading hydrogen peroxide. All these processes may result in increased oxidative stress. At increased level, superoxide can react with NO to form highly toxic peroxynitrite $ONOO^-$. This reaction decreases the availability of NO for *guanylate cyclase* resulting in reduced vasodilatation.

Figure 5. Involvement of hyperhomocysteinemia in oxidative stress and metabolism of fatty acids

Elevated homocysteine level was found in CVD risk patients as well as in depressed patients (Severus et al. 2001). However, several clinical trials using vitamin B supplements to correct hyperhomocysteinemia failled to reduce the risk for CVD (Baggott and Tamura 2015). Authors supposed a possible relation of Hcy to oxidative stress through association with „free iron“ (non-protein bound iron) which is involved in formation of homocysteine from methionine, S-adenosylhomocysteine and cystathionine leading to increased circulating homocysteine. „Free iron“ is involved in formation of reactive oxygen species (Ďuračková 2014) and oxidized low-density lipoproteins known as risk factors for damage to macromolecules in both, cardiovascular and psychiatric disorders, mostly in chronic conditions (Assies et al. 2014).

Another new risk factor for CVD and depression is being disscussed at present. Skaaby (2015) concluded that **vitamin D**, in addition to being an essential factor for bone mineralisation, at low level is associated with mortality and several diseases ranging from CVD to autoimmune and liver diseases. Sufficient level of vitamin D was defined as >50 nmol/L. Enhanced vitamin D level are associated with a decrease in triacylglycerols and very low density lipoprotein cholesterol.

Sub-optimal level of vitamin D was also determined in people with schizophrenia and other psychotic disorders (Berk et al. 2008, Menkes et al. 2012, Durmaz et al. 2016). As previously said, people with psychosis demonstrate high level of cardiovascular risk. However, detailed data are missing. In patients with psychotic disorders Lally et al. (2016) have found the negative association between vitamin D level and CVD risk factors such as waist circumference, triacylglycerols, total cholesterol, fasting glucose, Hemoglobin subunit alpha 1 and serum CRP levels. Significant association between depressive symptoms and physical condition in patients with chronic heart failure has been observed only in patients with vitamin D levels <50 nmol/L (Johansson et al. 2016). The reason for these associations is not quite understood. There is accumulating evidence that vitamin D deficiency may be associated with inflammatory processes. Negative correlations were observed in patients with diabetes mellitus between level of vitamin D and circulating concentration of proinflammatory IL-1 beta and IL-6, but not between TNF alpha and interferon gamma

(Tiwari et al. 2014). In patients with schizophrenia a negative correlation between vitamin D level and C-reactive protein was observed, especially in patients with elevated CRP (Zhu et al. 2015).

Depressed individuals in contrary to non-depressed subjects have one or more of these risk factors, and therefore the link between depression and CVD may be, in part, due to risk factor clustering (Joynt et al. 2003) (Figure 6). All this knowledge confirms the existence of a common underlying factor for both pathologies. This factor represents response based on dramatic dietary changes that occurred after the agricultural and technological revolution in the mid-19th century (Simopoulos, 2002) (Figure 6).

Figure 6. Potential mechanisms of the relationship between cardiovascular diseases and depression. Their relationship is based on changes in health status (physiological state) and in psychological states underlyined by factors causing both cardiovascular diseases and depression

Why are omega-3 FAs important for physical and mental health?

The physiological/pathophysiological effects of unsaturated fatty acids in the body are not the same. The main cause of the harmful effects of arachidonic acid in comparison with omega-3 FA is the formation of pro-inflammatory eicosanoids (Figure 7), whereas antiinflammatory eicosanoids are produced from the EPA. Structures of pro-inflammatory and anti-inflammatory eicosanoids consisting of AA, EPA and the precursor of AA synthesis, dihomo-gamma-linolenic acid (DGLA) are depicted in Figure 8. The proinflammatory eicosanoids have an even number of double bonds, while anti-inflammatory eicosanoids have an odd number of double bonds.

Figure 7. Synthesis of AA metabolites

Moreover, in addition to anti-inflammatory prostaglandins PGF1 (Figure 8), also other anti-inflammatory eicosanoids are synthesized from DGLA, such as e.g. thromboxane TXA1. From the omega-3 fatty acid, EPA, in addition to anti-inflammatory PGF3 there are synthesized also the anti-inflammatory eicosanoids such as thromboxane TXA3 and leukotriene LT5. Moreover, from the EPA and DHA by the catalytic action of *lipoxygenases* so-called resolvins and protectins are synthesized blocking the production of pro-inflammatory prostanoids. Resolvins were first described by Prof. Charls N. Serhan as oxygenation products of acids EPA (E series) and DHA (D series) that are present at sites of inflammation at nanomolar and picomolar concentrations. These substances have been isolated from the exudate of inflammatory site (resolving inflammatory exudate) (Serhan et al. 2005). In recent years resolvins have been studied particularly with regard to CVD. They are especially ethanolamide of docosahexaenoic acid (DHEA) and other derivatives inhibiting *COX2* similarly to acetic acid released from aspirin during *COX1* inhibition (aspirin-trigerred form of protectins, ATPD1). These compounds block the PMNLchemotaxis, they reduce expression of P-selectin, adhesion of leukocytes to the thromboxanes, in order to protect organs during ischemia-reperfusion injury (Alessandri et al. 2004). ATPD1 reduces transendothelial migration of PMNL and increases macrophage eferocytosis of apoptotic PMNL (Shinohara et al. 2012). Further experiments could clarify whether these anti-inflammatory and immunoregulatory reactions find application in the inflammatory responses of the nervous tissue in the brain.

Figure 8. Metabolites of AA, EPA and DHA

Omega-3 fatty acids may contribute to the protective effects on cells of the CNS not only by biochemical processes but also by mechanical / biophysical mechanisms. Fatty acids are part of phospholipids and in this form they are part of cell membranes. The composition of lipids in the membranes affects the important property of membranes - the fluidity (flowability) of nerve cell membranes. Under the fluidity of the membrane we mean the free movement of FA hydrophobic chains in the bilayer of a biological membrane. Residues of FA chains within the membrane may perform different movements depending on the structure (chain length, number of double bonds) - flexion, rotation, lateral diffusion, bobbing and flip-

flop (Figure 9). Generally, improved fluidity of the membrane is associated with a reduction of the ratio of saturated phospholipid to unsaturated, sphingomyelin to phosphatidylcholine, cholesterol to phospholipids (Yao and van Kammen 1994). Longer polyunsaturated FA fluidize membranes more than shorter FA (they need more space for the oscillating motion of the hydrophobic chain in the membrane). Moreover, a longer FA embedded in the membrane (e.g. DHA) contributes to the increased size of lipoprotein particles LDL and HDL characterized by an atheroprotective effect (Oravec et al. 2011, Muchová et al. 2016).

Figure 9. Movement of hydrophobic chains of fatty acids in a biological membrane

In addition to the composition of FA, membrane fluidity is influenced also by other factors, e.g. oxidative damage, presence of cholesterol, presence of membrane proteins or saccharides and temperature. A change in the membrane fluidity results in a change in membrane properties, such as density and binding affinity of neurotransmitters and neurohormones, including serotonin, norepinephrine and dopamine. Conversely, fluidity affects the function of proteins embedded in the membrane (receptors, transporters), and thus the function of the membrane.

Key protective effect of DHA might be related to its spatial characteristics. The increased number of carbons and six double bonds in the DHA molecule (22:6), as reported above, needs more space for its existence in a membrane than EPA, thereby increasing the fluidity of the membrane, which is critical especially for the synapse, and is needed for the rotation of receptors and signal transmission from the membrane surface inside a nerve cell (Stillwell and Wassall 2003).

EPA is present in the brain only in small quantities, so initially it was assumed to have no significance for proper brain function. However, EPA may improve some mental disorders and has a role in brain function. The most important function of the EPA in the brain is the inhibition of the inflammatory response and the stimulation of cell signaling mediated by anti-inflammatory eicosanoids. In addition, EPA competitively inhibits different desaturase, than DHA, *delta-5 desaturase* (D5D), necessary for the synthesis of AA. EPA is also a competitor

for the incorporation of AA into membranes of nerve cells, but also for *phospholipase 2*, catalyzing the release of AA from membranes. By the inhibition of AA production and its release from membranes the formation of inflammatory eicosanoids is inhibited (Figure 10).

Figure 10. Mutual relation of LA and ALA metabolites

Less information is available about the relationship between the pathophysiology of the depressive disorder, and cardiovascular diseases in children (Tonhajzerová and Ondrejka 2008). Epidemiological studies indicate a protective role of omega-3 FA against CVD in adults. In children, their potential beneficial effect for insulin sensitivity in boys but not in girls (Burrows et al. 2011) and blood pressure control (O'Sullivan et al. 2012) were observed. Mechanisms through which omega-3 FA act are not quite known. But it is supposed that interaction with ion channel and influence on plasma membrane fluidity are involved. Omega-3 FA can act also as competitors for cytochrome P-450 with respect to omega-6 FA and thus can modulate the biosynthesis of eicosanoids with protective action. The complex interactions of different nutrients including polyunsaturated FA and polymorphism in genes involved in omega-3 FA metabolism should be kept in mind (Bonafini et al. 2015).

Studies examining the antidepressant effects of individual nutritional supplements in children and adolescents are also assessed (Lopresti 2015). The antidepressant effects of omega-3 FA are believed to be derived from one or several of its biological effects: (1) antiinflammatory effect through decreasing of pro-inflammatory mediators (Grosso et al. 2014), (2) modulation of synaptic plasticity and enhanced neurotransmission (Crupi et al. 2013), (3) increasing of membrane fluidity (Avorech et al. 2015), (4) influencing of hypothalamus-pituitary adrenal axis activity through cortisol regulation (Barbadoro et al. 2013). All these potential pathophysiological mechanisms can be also applied in CVD.

The preliminary positive support for the antidepressant effects of omega-3 FA for youth depression is provided from only two studies (Nemets et al. 2006, McNamara et al. 2014). Results from our study with 35 depressive children and adolescents supplemented with fish oil emulsion rich in omega-3 FA indicate the reduction of depressive symptoms evaluated

as CDI score after 3 months intervention (Trebaticka et al., accepted by Child Adolesc Psychiatry Ment Health).

Correlation between the impact of omega-3 FA on the pathophysiology of CVD and depression was also manifested in the study of the impact of omega-3 FA on lipid profile. Our results from the study of the effect of emulsified mixture of plant sterol esters (1.3 g), fish oil (1 g EPA+ DHA), vitamin B12 (50 μg), B6 (2.5 mg), folic acid (0.8 mg) and coenzyme Q10 (3 mg) on lipid profile of hypercholesterolemic children indicate the increased anti-atherogenic IDL3 and LDL1 and reduced atherogenic ILD2 subfractions (Garaiova et al. 2013). In another study of ours with 35 depressive children and adolescents an increased anti-atherogenic large HDL subfractions and decreased atherogenic small HDL subfractions were observed after 3 months supplementation with emulsion of fish oil rich in omega-3 FA (unpublished results).

Although results of the impact of omega-3 FA from meta-analyses are sometimes contradictory, positive effect on physical and mental health is unambiguous. However, various professional societies differ in the recommendation of appropriate doses and duration of omega-3 FA supplementation for both CVD and mental health (Graham et al. 2007, Vrablík et al. 2009).

For the Europeans daily recommended dose of DHA and EPA is 300-600 mg for the primary prevention and 900-1200 mg for the secondary prevention, minimum daily dose for adults is 250 mg EPA+DHA, for pregnant women is 200-300 mg, for children aged 7 – 24 months – 100 mg DHA, children aged 2 – 18 years – 250 mg EPA+DHA (Simopoulos 2002, Grosso et al. 2014, Gow and Hibbeln 2014). The recommended intake of omega-3 FAs can be reached by the consumption of fish (preferably fatty fish such as salmon, mackerel, tuna, sardines) twice a day. However, to reduce TAG the intake of omega-3 FA must be increased to 3-4 g of per day.

The question is the appropriate ratio of EPA and DHA in the supplements used and supplement forms - capsules or oils or oil emulsions. In the case of CVD recommended ratio EPA:DHA is 1:2; for mental disorders recommended composition of supplement is at least 60% EPA and 40% DHA. It is recommended to follow instructions in the leaflet inserted in supplement packages and check supplement composition (ratio of EPA and DHA). Capsules and emulsions have not the same ability to be absorbed through the digestive tract. Omega-3

FA from the emulsions are better absorbed compared to the uptake of triacylglycerols from fish oil contained in capsules. Moreover, the emulsion can be adjusted to the desired flavor and taste and in the emulsified form the access of *lipases* (enzymes necessary for the release of fatty acids from lipids) to the lipids is improved (Garaiova et al. 2007, Raatz, 2009).

Conclusions

Depression and CVD are linked through some pathophysiological events. Their relation is bi-directional. Depression not only increases, but also predicts the risk of adverse cardiovascular events in patients with established heart disease, but it also predicts incidence of CVD in individuals with no history of cardiac problems. On the other hand, CVD influence affective states and may induce depression. Specific neurophysiological and behavioural abnormalities have been observed in depressed patients, which may account for the relationship to CVD. This mutual relation may be mediated via the pathophysiological pathways that are shared between CVD and depression, like neurohormonal activation, rhythm disturbance, inflammation and hypercoagulability. Each of these areas of interconnection represents a potential therapeutic intervention to improve both, CVD and depression.

However, better understanding of the links between depression and CVD will require large and well designed clinical trials with assembling of both, physiological and behavioral outcomes. Obtained results could explain open questions and improve quality of life, reduce time of hospitalization, decrease mortality and last but not least can reduce the economic burdens incurred in relation to CVD and psychiatric disorders.

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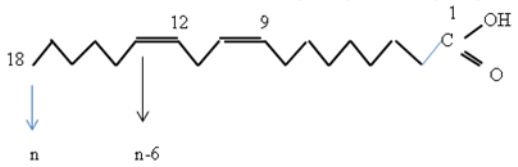
Figure 1. Essential fatty acids

Linoleic acid – LA - 18:2 (9,12) - n-6 (**ω-6**)



Linolenic acid – ALA (alfa-linolenic acid) - 18:3 (9,12,15) - n-3 (**ω-3**)

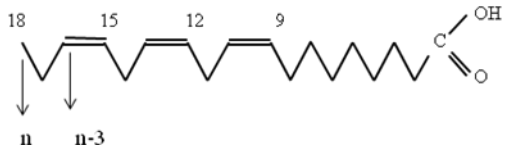


Figure 2. Polyunsaturated fatty acids synthesis from linoleic acid and linolenic acid

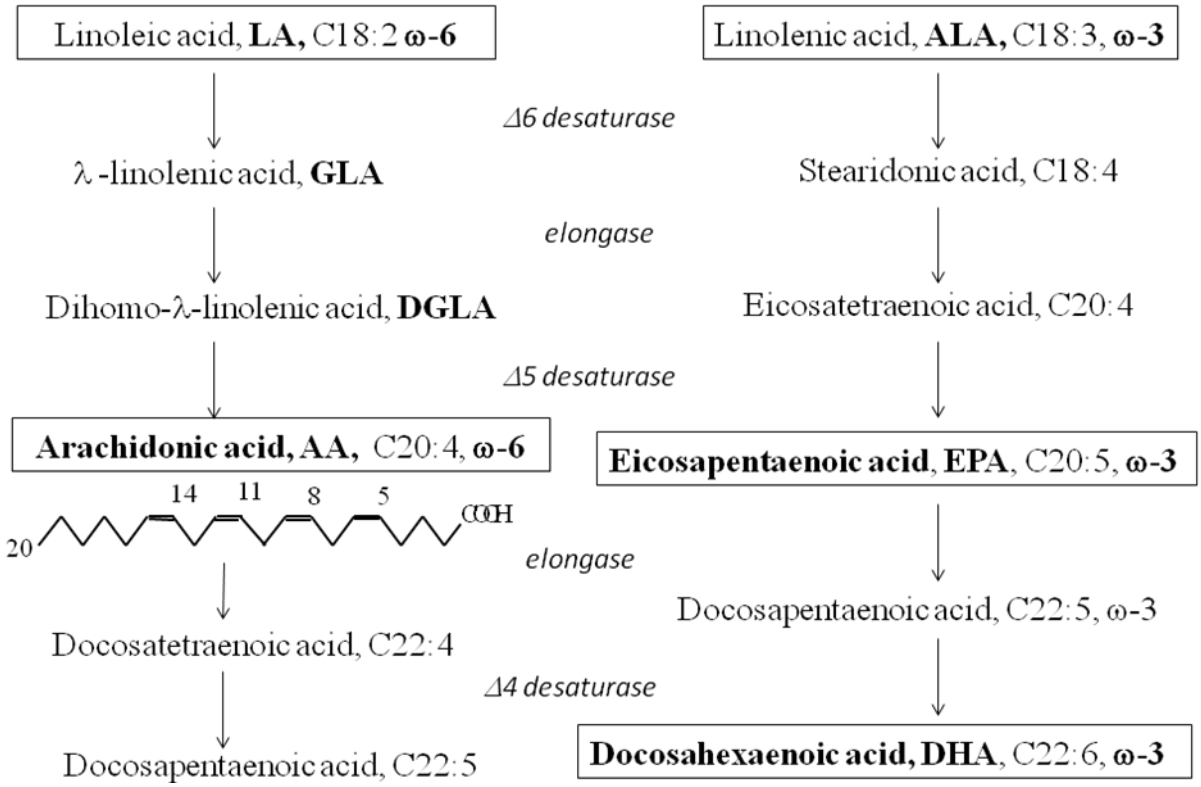


Figure 3. Fatty acid metabolism

AA – arachidonic acid, BBB – blood brain barrier, DHA – docosahexaenoic acid, LA – linoleic acid, ALA – alpha linolenic acid, FABP – fatty acid binding protein, GFL – glycerophospholipid, TAG – triacylglycerol, VLDL – very low density lipoprotein

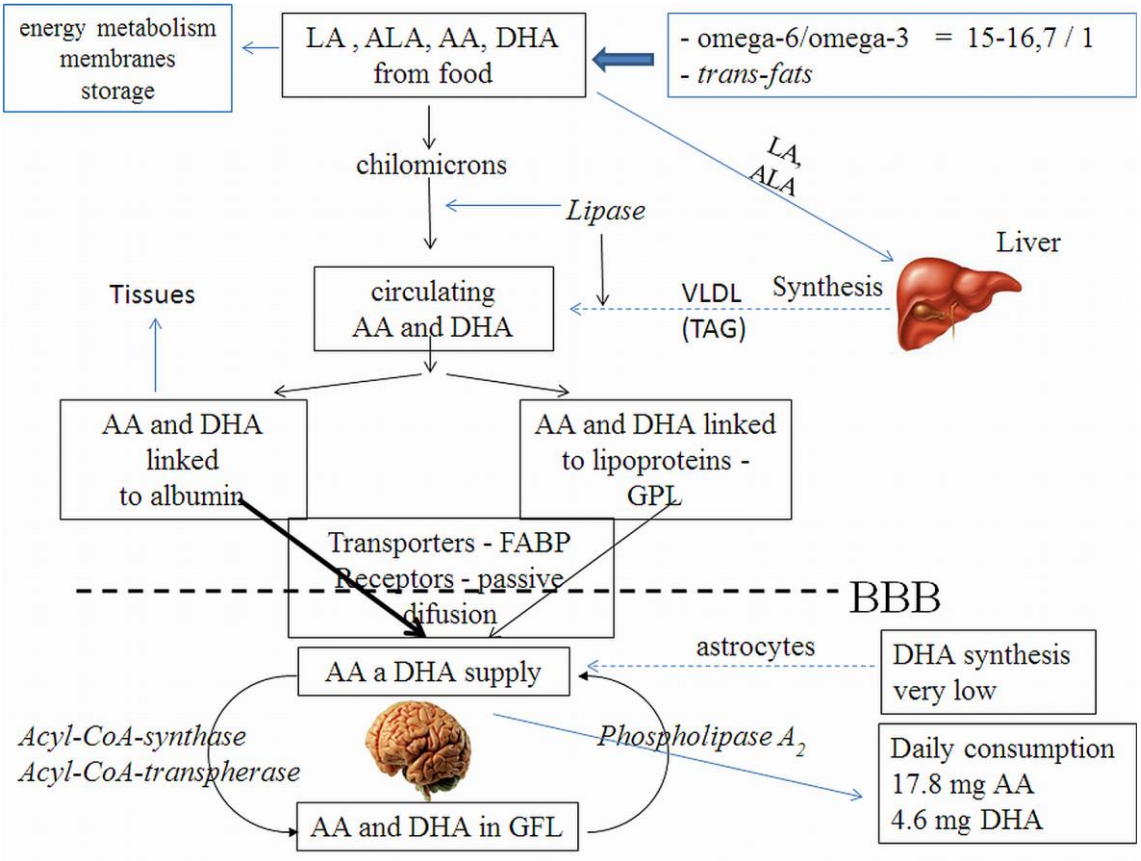


Figure 4. Pathophysiological characteristics of cardiovascular diseases and depression disorders

CVD – cardiovascular disease

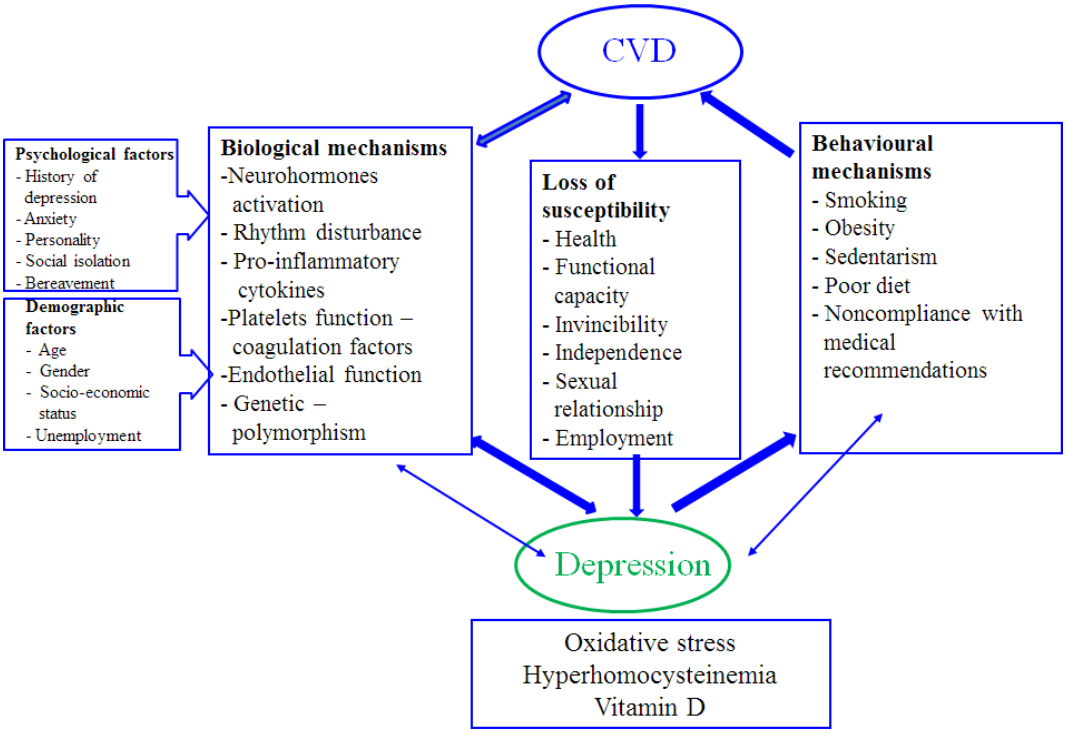


Figure 5. Involvement of hyperhomocysteinemia in oxidative stress and metabolism of fatty acids

ADMA – asymmetric dimethylarginine, DNA – deoxyribonucleic acid, GPx – *glutathione peroxidase*, GSH – reduced glutathione, Hcy – homocysteine, NOS – *nitroxide synthase*, Om-3 – omega-3 fatty acid

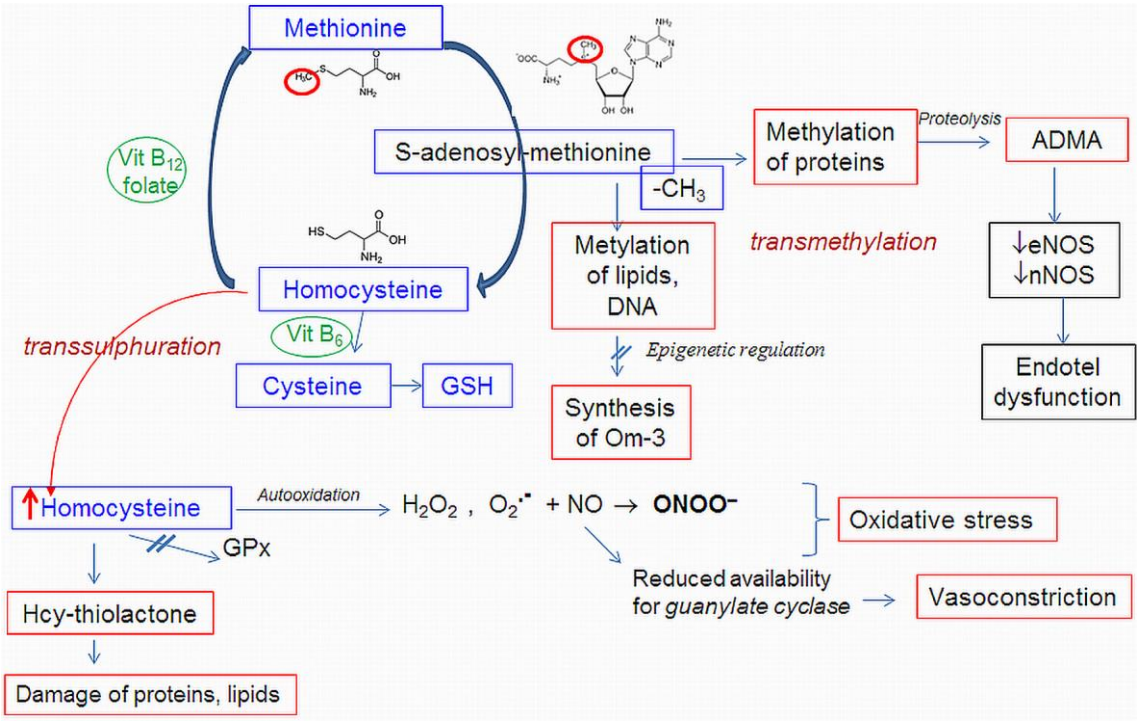


Figure 6. Potential mechanisms of the relationship between cardiovascular diseases and depression. Their relationship is based on changes in health status (physiological state) and in psychological states underlyined by factors causing both cardiovascular diseases and depression

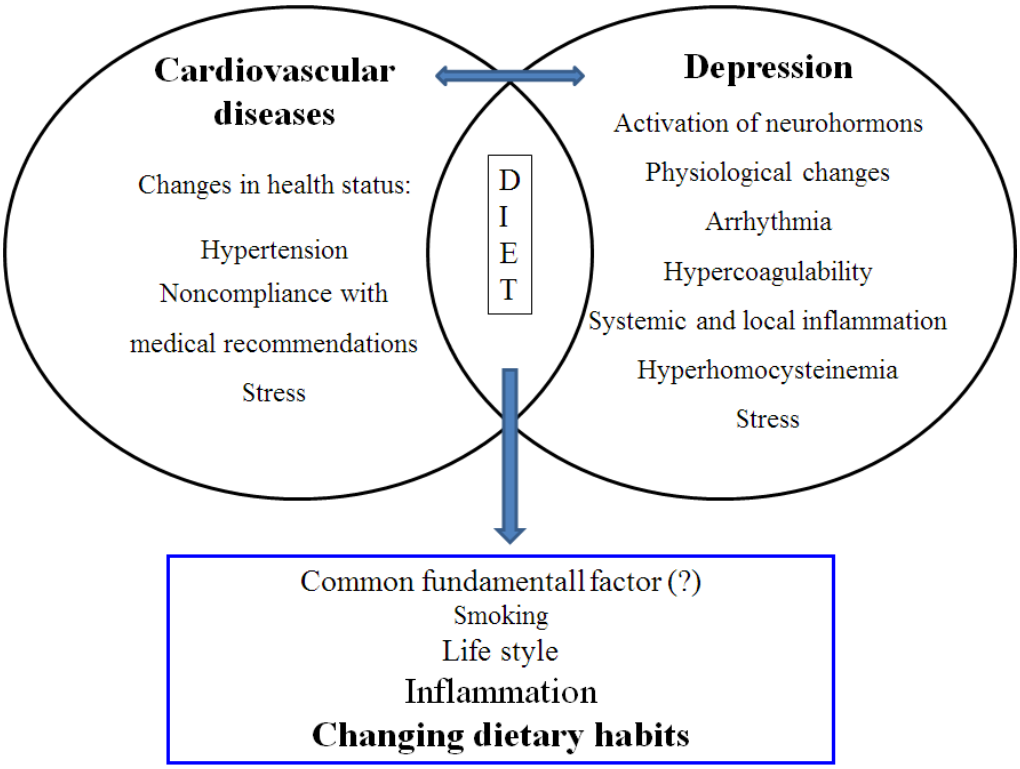


Figure 7. Synthesis of AA metabolites

COX – *cyclooxygenase*, LOX – *lipoxygenase*, PG- prostaglandin, TX – thromboxan, PGI – prostacyklin, LX – lipoxin, LT – leukotriene, HPETE – hydroperoxyeicosatetraenoic acid, HETE – hydroxyeicosatetraenoic acid. Circled prostaglandin PGE2, thromboxane TXA2 and leukotriene LTB4 have the largest pro-inflammatory effects

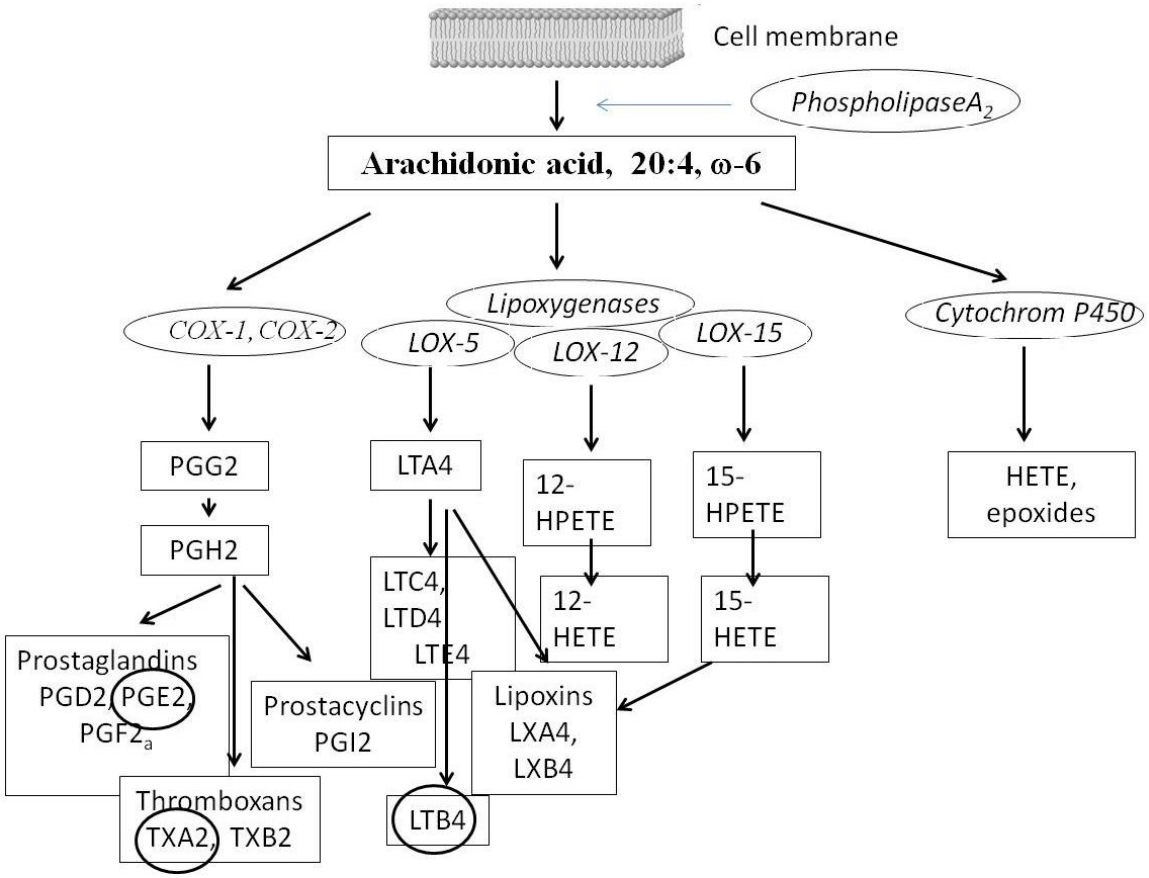


Figure 8. Metabolites of AA, EPA and DHA

PGF – prostaglandin F, AA – arachidonic acid, EPA – eicosapentaenoic acid, DGLA – dihomo-gama-linolenic acid

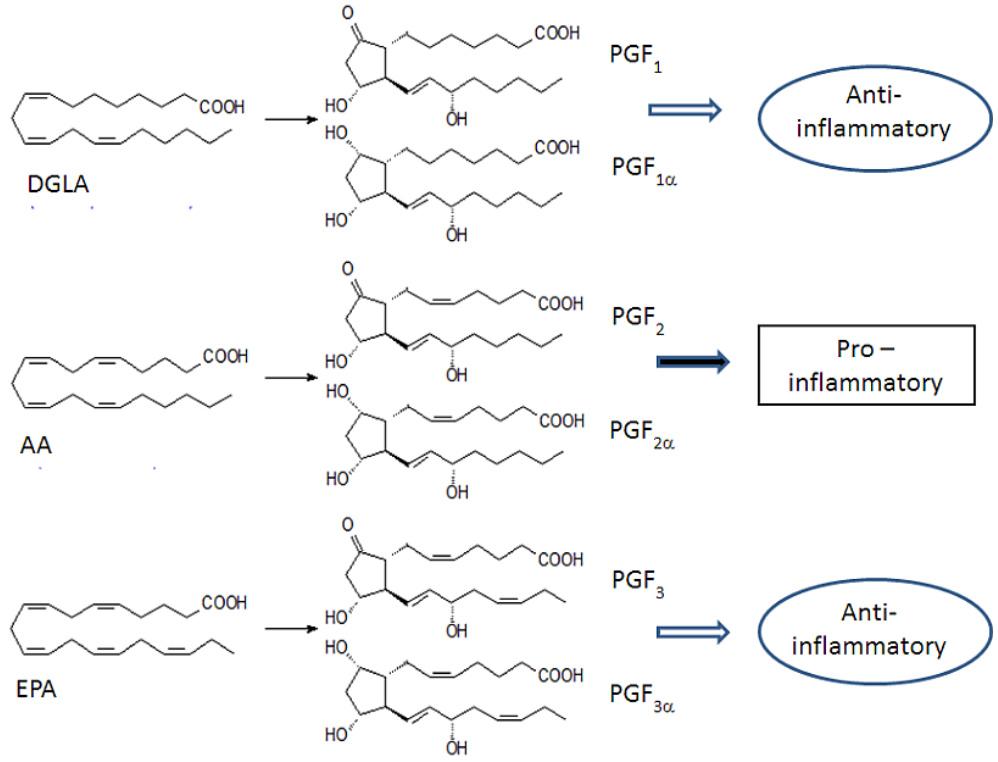


Figure 9. Movement of hydrophobic chains of fatty acids in a biological membrane

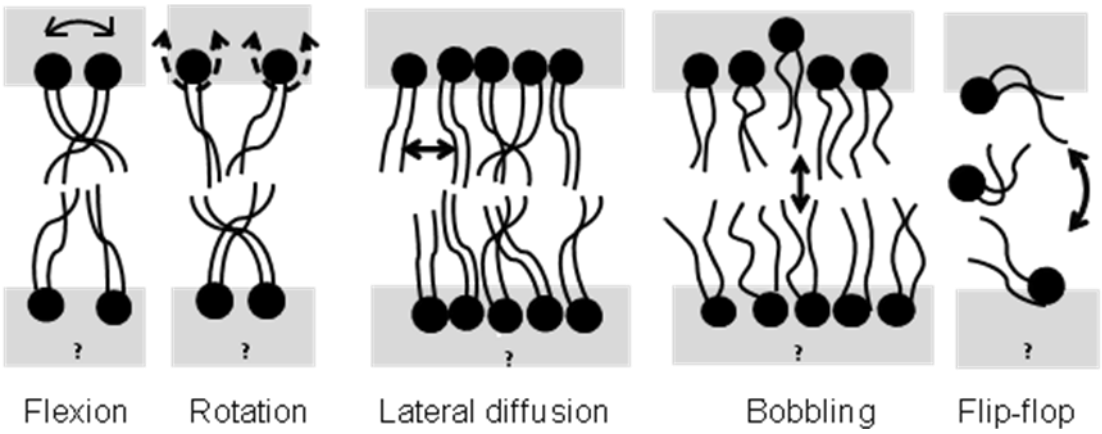


Figure 10. Mutual relation of LA and ALA metabolites

ALA – alpha linolenic acid, COX – *cyclooxygenase*, D4D – *delta-4-desaturase*, D5D – *delta-5-desaturase*, D6D – *delta-6-desaturase*, DGLA – dihomo-gama-linolenic acid, DHA – docosahexaenoic acid, EPA – eicosapentaenoic acid, GLA – gama linolenic acid, LA – linoleic acid, LT – leukotriene, LOX – *lipoxygenase*, PG – prostaglandin, PhL – *phospholipase*, TX – thromboxane