EFFECTS OF LONG-CHAIN POLYUNSATURATED FATTY ACIDS (LCPUFA) ON HUMAN HEALTH

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Human body is capable of producing various types of fatty acids from other fats as well as from other substances (raw materials). However in case of omega-3 fatty acids, it does not happen because they are not made in the body and are supplied with the food that is why they are essential fatty acids. Foods high in Omega-3 include fish, vegetable oils, nuts (especially walnuts), flax seeds, flaxseed oil, and leafy vegetables.

What makes omega-3 fats special? They are an integral part of cell membranes throughout the body and affect the function of cell receptors in the membranes. They provide the starting point for making hormones that regulate blood clotting, contraction and relaxation of artery walls, and inflammation. They also bind receptors in cells that regulate genetic function. Likely due to these effects, omega-3 fats have been shown to help prevent heart disease and stroke, may help control lupus, eczema, and rheumatoid arthritis, and may play protective roles in cancer and other conditions. (1)

WHAT ARE THE TYPES OF OMEGA-3 FATTY ACIDS?

There are three main omega-3s:

— Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA and DHA are found in fatty fishes such as herring, mackerel, salmon, tuna and trout.

— Alpha-linolenic acid (ALA), (the most common omega-3 fatty acid in most Western diets) the human body generally uses ALA for energy, and conversion into EPA and DHA is very limited. ALA is found in flaxseed, canola and soybean oils, and walnuts. (2)

All omega fatty acids play specific roles in overall health. Speaking about the effects of polyunsaturated n 3 fatty acids on different aspects of human health it is worth to note that there are a great deal of works dedicated to this theme from one hand and deviations and ambiguity of opinions on the other hand.

Nevertheless there are evidence that suggest that these LCPUFA can have health benefits, including:

— Prevent coronary heart disease;
— Prevent stroke;
— Prevent diabetes;
— Promote healthy nerve activity;
— Prevent cancer;
— Improve vitamin absorption;
— Maintain a healthy immune system;
— Promote cell development (3, 4, 5).

Supply of polyunsaturated omega-3 fatty acids into the body is associated with adequate consumption of fish, which also contains essential amino acids, vitamins and mineral substances a person needs to stay healthy. However in Germany the consumption of fish is much lower than consumption of meat. In 2012 the consumption of fish per person came to 14.4 kg (basing on the weight of the caught fish). (6). German Nutrition Society (DGE) recommends in this connection a weekly consumption of 80 – 150 gram of not oily fish (salmon, sea bass, cod) and 70 gr of oily fish (herring, mackerel). (7) It corresponds to 15 kg of white fish and 7,3 kg of oily fish per person per year. (8) Correspondingly, the consumption of an average German citizen is lower than recommended.

High blood pressure (HBP), hyperlipidaemia, inflammation and Diabetes Mellitus are serious risk factor for cardiovascular disease. Since numerous researches refer to a positive effect of omega-3 fatty acids DHA and EPA of sea origin on HBP, most researches have focused on investigation of the influence of fish oil on the progression of these very processes (9, 10, 11).

There are also works confirming the positive effect of omega-3 fatty acids DHA and EPA on frequency and clinical course of oncologic diseases (especially on the GI tumours) due to reduction of anti-inflammatory effect and the influence of eicosanoids and omega-3 on proliferation of cells. (12, 13, 14, 15, 16). However, number of authors indicate on a higher risk of incidence of prostate cancer due to consumption of omega-3 fatty acids DHA and EPA. (17, 18, 19, 20).

It is not always simple to differentiate the effect of omega-3, since fish contains as well fat-soluble vitamins and microelements possessing their own effects (e.g. vitamin D and selenium). In Germany there are people who do not eat fish or eat fish moderately (21). According to the consumption statistics about 16% of respondents do not eat fish. It might be accounted for ethical problems among vegans or vegetarians or the danger of contamination of sea products with compounds of mercury and dioxin, high concentrations of which might be found there in substantial qualities. Maximum permissible dose limits for mercury compounds in Germany is defined as 1,0 mg/kg (22). Highest concentrations of mercury compounds are found in tuna (0,9 mg/kg) and black halibut (1,03 mg/kg). This toxic compound is accumulated in the body and may cause Minamata disease. Thus, it is not recommended to eat fish in the amounts that exceed DGE recommendation, but not to give up eating fish due to high concentrations of omega-3 despite of relatively moderate concentrations of methylmercury (0,5 mg/kg) in some fish species, such as herring.

INFLUENCE OF POLYUNSATURATED OMEGA-3, 6 FATTY ACIDS (LCPUFA) ON DEVELOPMENT AND FUNCTIONING OF BRAIN, DEVELOPMENT OF VISUAL PERCEPTION AND COGNITIVE ABILITIES

There are practically no arguments among specialists regardiong prescription of omega-3, 6 fatty acids during pregnancy for optimal development of cognitive abilities and visual perception of an embryo (23, 24), as well as prescription in the long run for a positive effect on child's sleep and development of fine motor skills (25, 26, 27, 28). However, actual researches still question these effects and confirm so far only positive effect of omega-3, 6 fatty acids during infant's first moths and the influence later is evaluated as not significant. (29)

To what extent these results are true, will be testified by future researches but at present a daily intake of minimum 200 DHA is recommended to pregnant and breast feeding women for optimal development of the embryo and infant. If it is impossible to supply the required amount of DHA with fish intake, it might be consumed as dietary supplements. (26, 30)

Long-chain polyunsaturated omega-3 fatty acids DHA and EPA (LCPUFA) are essential elements for building, forming and physiological formation of nerve fibres (31). And this influence occurs long before the birth. Already in the third trimester of pregnancy the DHA begins to build up into the structures of embryo's brain and this process is going on during the first two years of life. (32, 33). Optimal development of the nervous system depends on adequate supply of long-chain polyunsaturated fatty acids (LCPUFA) (31). Most important role for development and formation of brain play DHA and Arachidonic acid (AA) (omega-6), which is supplied to exclusively breastfed infants together with other polyunsaturated omega-3, 6 fatty acids (34, 35, 36, 37). Especially high proportion of DHA, EPA and AA is revealed in phospholipids of cellular membrane of brain and retina (31). 10–15% of an adult brain consists of DHA.

Along with numerous integral functions polyunsaturated omega-3, 6 fatty acids play a crucial role in the functioning of the nervous system. Therefore, they affect formation and action of such neurotransmitters as serotonin, noradrenaline and dopamine. They also regulate intercellular (synaptic) signal reduction. Through this action modulation of basic processes such as memory, cognition, emotions, cycles of sleep, perception of pain, sexual behaviour takes place. (32, 38, 39, 40, 41, 42, 43).

Increase of DHA proportion in phospholipids membranes of nervous cells due to change of physical and chemical properties increases «fluidity» (penetration) of membranes. This, in its turn, activates receptors connected with the membrane and transport proteins, and finally induces transmission of a signal between nervous cells. (40, 41) Omega-3 fatty acids plays not a lesser role in complex processes in the nervous system as e.g. adaptation of the nervous system to external exposure (neuroplasticity) or regulation of neuronal gene expression. 38, 39, 40, 41, 42, 43, 44, 45).

Despite of the fact that data was collected from animal experimentation, the latest investigations confirm its relevancy for humans (23, 46)

The second place on DHA contents after the brain is occupied by the pigmented layer of retina and photoreceptor cells, where DHA possibly influences the projection of optical stimulation of subcortical centres (23).

Since recently the possibility of a protective role of DHA in pathophysiology of aged-related macular degeneration has been considered) (24).

The adequate consumption of polyunsaturated omega-3 fatty acids is necessary for correct formation of these structures during pregnancy. (23).

One more research question is the role of omega-3 fatty acids DHA and EPA in cognitive functions and occurrence of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and neuropsychiatric disorders (bipolar disorder, borderline personality disorder, schizophrenia, depressions).

Cerebral circulation is the most important factor affecting functioning of the brain. Due to a high energetic demand and relatively low storage capacity of energetic substrate the condition of cerebral vessels is decisive for its normal functioning. (46)

The quality of blood supply to the brain directly correlates with neurodegenerative and cerebrovascular diseases such as atherosclerosis, stroke and vascular dementia.

We have already mentioned numerous evidence on the impact of increased concentration of DHA on the condition of cerebral vessels and its result on cerebral circulation (46, 47), which is true both for animal and people. (48, 49)

A possible mechanism of effects on cerebral vessels is DHA interaction with acetylcholine receptors and induction of NO synthesis by means of which the increase of NO results in vasodilatation.

There is DHA dependant enhancing of cerebral circulation in the cerebral fissures and thalamus, which play a key role in general thought (cortex), as well as in development of personality and consciousness (50)

Latest researches (50) has shown that damages of blood circulation particularly in this areas of brain triggers incidence of Alzheimer's disease, dementia and decline of cognitive abilities in elderly people. Researchers revealed that increased DHA transportation in the body results in increased DHA concentration in the membranes of nervous cells which affects the fluidity and permeability and consequently changes the activity of membrane membrane-bound proteins. (40, 41).

Long chain omega-3 fatty acids, especially, DHA provides a marked influence on development, structure and physiology of the brain and evidently on blood circulation which is of key importance for neuropsychiatric and neurodegenerative diseases.

To demonstrate this correlation the model of Haast and Kiliaan was proposed (46), which comprise three compounds of brain health (structure, function and blood circulation). Basing on this model, LCPUFAs optimally impact all compounds of this model: quality of the structure, function and blood circulation meanwhile saturated fatty acids produce an opposite action.

Pathophysiological role of neuroprotection D1 (NPD 1) is well-documented. It is synthesised in the brain structures (24) and has a protective action on neurons.

This is manifested in antiapoptotic and anti-inflammatory properties and also in strengthening neural resistance against oxidative stress. (51, 52). Besides NPD 1 reduces production of the β-amyloid (51), which is the part of senile plaques, metabolism damage, which is along with other factors such as the phosphorylation of the microtubule-associated protein tau, weakening of antioxidative reserves and presynaptic cholinergic deficit constitute the main morphological peculiarity of Alzheimer and other dementia illnesses. Therefore, we can postulate that deficit of DHA due to reduction of NPD 1 production may contribute to the development of these illnesses. 53)

THE INFLUENCE OF POLYUNSATURATED FATTY ACIDS (PUFA) ON CARDIO-VASCULAR SYSTEM

Food ratio impacts health by means of a series of biological mechanisms. From one point it implies reduction of lipids and their subfractions in blood plasma. From the other point it is an important impact on blood pressure, thrombophilia, endothelial function and oxidative stress. (Thomas Stulnig, Ernährungsumschau (2015).

In the last years the attention of researchers was focused on the problem of subclinical inflammatory reaction, which is closely connected with the development of cardiovascular disease and its complications, Diabetes mellitus 2 and depends greatly on food. (54)

For better understanding the example of Mediterranean countries may be considered where relatively low level of cardiovascular illnesses is observed. This can be attributed to high consumption of vegetable oils (olive oil which contains simple unsaturated fatty acids) with relatively high consumption of fat. Complemented with a high level of carotenoids, secondary vegetative substances and water soluble dietary fibres, which signals adequate consumption of vegetables and fruits, meanwhile such a diet provides preventive impact on atherosclerotic illnesses.

Research PREDIMED conducted in 2013 (55) showed, that a diet may radically change the level of cardiovascular disease. In this research it was found out that relatively rich in fat Mediterranean diet containing olive oil and nuts reduces cardiovascular risk (myocardial infarction, stroke or death from cardiovascular illnesses) by 30% in comparison with a lower in calories and fat diet. On the other side low-fat diets often do not lead to reduction of cardiovascular

illnesses. (56). It allows to conclude that the quality and not the quantity of fat is decisive for development of cardiovascular illnesses.

Among polyunsaturated fatty acids (PUFA) the most biological impact is provided with omega-3 fatty acids DHA and EPA (C20 or C22), from which mediators (eicosanoids) with anti-inflammatory action are synthesised. Eicosanoids is a general group of physiologically and pharmacologically active compounds containing prostanoids (prostaglandins, prostacyclins, thromboxane) and leukotrienes. They have a very short life (are destructed within a few seconds), that is why they produce effects as "hormones of local action".(57). Most interesting from anti-Inflammatory point of view are derivates of omega-3 fatty acids DHA and EPA resolvin and protectin, two new families of bioactive mediators, termed resolvins and protectins, biosynthesized from omega-3 essential PUFAs.

Resolvins control inflammation at many levels, by reducing peritonitis and skin inflammation, protecting organs from reperfusion injury and neovascularization. Thus, D-series resolvins are of interest in the control of inflammation-resolution in host defence and in neural tissues (58).

DHA is converted in resolving exudates to another new family of mediators named protectins. Mediators of this family are distinguished by the presence of a conjugated triene double bond system and their potent bioactivity. They are biosynthesized via a lipoxygenase mechanism that converts DHA to a 17S-hydroperoxide-containing intermediate, which is rapidly converted by human leukocytes into a 16(17)-epoxide that is enzymatically opened in these cells into a 10,17-dihydroxy-containing anti-inflammatory molecule. This bioactive compound, initially coined 10,17-diHDHA or 10,17S-docosatriene, is now known as protectin D1 owing to its potent protective activity in inflammatory and neural systems documented in studies with N. Bazan and colleagues. It is termed neuroprotectin D170 when produced by neural tissues; the prefix neuro is added to signify its biosynthetic origin (59, 60, 61, 62).

Several 10, 17-dihydroxy-containing products are produced in vivo via different biosynthetic routes, the most potent being protectin D1. The other natural protectin D1 isomers have different double-bond configurations and are less potent in dampening neutrophil recruitment and inflammation. Protectin D1 is stereo-selective and log-orders of magnitude more potent in vivo than its precursor DHA. Protectin D1 is also produced by human peripheral blood mononuclear cells in T helper-2-type conditions in a lipoxygenase-dependent manner via a 16(17)-epoxide intermediate. Protectin D1 blocks T-cell migration in vivo, reduces TNF and interferon-γ secretion, and promotes T-cell apoptosis (63).

Protective attributes of long chain (more than C20) omega-3 essential PUFAs are probably connected with a number of molecular mechanisms including anti- inflammatory effects (64, 65, 66, 67). On the clinical level such effects due to intake of omega-3 essential PUFAs as anti-arrhythmic and hypotensive actions with relatively low dosages (from 1 gr per day) (66). On the opposite, such properties as reduction of triglycerides in the serum depends from the dose. Additional protective effects include neurovegetative changes, improvement of endothelial function and decrease of vascular resistance and in high doses changes in thrombocyte function is observed (68, 69, 70, 71, 72, 73).

It is interesting to note the difference in action between omega-3 fatty acids DHA and EPA and omega-6 fatty acids LA and AA.

Above described mechanisms of PUFA cardioprotective effect are characteristic of omega-3 fatty acids DHA and EPA but not of omega-6 fatty acids LA and AA. The review of all randomised investigations shows reduction by 19% in CHD risk reduction after increasing intake PUFA (74).

An increase of dosages of exclusively omega-6 fatty acids LA and AA shows on the opposite an increase of the risk. Clinical data give evidence on the benefits of omega-3 fatty acids DHA and EPA for prevention of illnesses. A low level of EPA in the serum correlates with a higher risk of atherosclerotic changes in the coronary vessels. Serum concentration of omega-6 fatty acids does not correlate with vascular changes in the heart vessels. A similar connection was revealed between the frequency of subclinical strokes, diagnosed by magnetic resonance imaging, and a high level of DHA and EPA (75). The finding of Thies et al. (76) in a randomised research showed significant qualitative reduction of macrophages after intake of omega-3 fatty acids (cod liver oil) unlike omega-6 fatty (sunflower oil) in comparison with the control group.

It is noteworthy to mention that α-Linolenic acid, which is often called «plant omega-3 unsaturated fatty acid» do not produce a protective effect on cardiovascular system (cc3). On the opposite, omega-3 fatty acids DHA and EPA from cod liver oil produce a protective effect, which can be reproduced in the researches (66).

In the GISSI-Prevenzione trial, with participation of 11000 post myocardial infarction patients, were administered to 1 gram of DHA and EPA as compared to placebo with intake of vitamin E (randomised). However, as after intake of vitamin E no positive effects were reported, after intake of omega-3 fatty

acids the reduction of mortality level, myocardial infarction without mortality and stroke by 15%, as well as mortality from cardiovascular diseases by 30% were observed. (77). This effect is especially manifested on cases of sudden deaths, the level of which reduced by 50%, which is of great importance for this vulnerable cohort. Similar effects were observed in Japan in the patients for whom statins are prescribed. (JELIS studio). (78) In this case EPA daily doses were 1800 mg and the study lasted 5 years. The data showed that levels of myocardial infarction, unstable angina pectoris, cardiac bypass, angioplasty and stenting was reduced by 19% (p = 0,011)

In other works (79) was noted that Alfa Omega Trial (223 mg EPA plus 149 DHA) has an anti-arrhythmic effect even in relatively low doses. This effect was confirmed in Meta-analysis too. (10, 13, 80)

Thus, we can make a conclusion that a decisive role in the efficacy of food fats belongs to their quality. Long chain omega-3 fatty acids DHA and EPA that are found in cod liver oil produce a protective effect in cardiovascular diseases (unlike shorter chain plant-based omega-3 fatty acids and omega-6 fatty acids LA and AA), which allows to recommend these preparations to patients for prevention of cardiovascular diseases. (81)

AGE RELATED COGNITIVE DECLINE

Aging facilitates reduction of neurons, synapses and brain volume (82), which in its turn leads to decline in cognitive abilities (83). Reduction in grey matter begins after twenties and in the white matter after forties. DHA concentration in the brain substance is also constantly decreasing. Therefore, it can be imagined that due to neurophysiological functions DHA acts as a neurotropic growth factor (84), which improves brain neuroplasticity and stimulates production of synapses (85, 86)

Despite of all mentioned above there are a very few studies that give evidence to the effect of LCPUFA supplementation on cognitive abilities in elderly people, (87), most of the studies were carried out on animals (88, 89). The available human data shows increase in grey matter and increase in brain volume as response to DHA supplementation.

However in these studies there are no clinically relevant endpoints and they are limited to radiological measurements of brain volume. Interesting that DHA supplement to the ratio especially significantly impacts the grey matter, so called cortico limbic system, the area of the brain which presents a functional unity of brain structures responsible for emotionally motivated behaviour, such as nutritional, sexual, defensive instincts. This system is involved in sleep-wake cycle. Impairment in functioning of this area may probably lead to various psychic pathologies. Studies showed that increase of the doses of trans-unsaturated fatty acids in healthy adults may cause reduction in brain atrophy (90).

A few human studies, we have at our disposal, which demonstrate the impact of either DHA or DHA+ EPA on cognitive abilities of elderly people contain contradictory findings (91, 92, 93, 94, 95, 96).

In the work Abubakari et al. (97) are given data on memory improvement due to a low dose supplementation of DHA+ EPA (<1,7 g/d), at the same a higher dose (> 1,7 g/d) was not associated with the effect. (97)

Nevertheless, Cochrane Metaanalyse (2012) reveals no influence of supplementation on improvement of cognitive abilities and reduction of dementia incidence in healthy people after 60 (98).

It is difficult to evaluate reliability of the conclusions because certain factors were not accounted: such as the differences between different omega 3 fatty acids, cod liver oil (mono and combined preparations), between Alzheimer's and other dementia forms. Authors of the actual meta-analysis (2015) basing on more than 15 intervention studies indicate that DHA supplementation of 500–1000 mg/d (50,2) may improve episodic memory in healthy people. This conclusion is valid only in regard to healthy respondents with mild memory complains but by no means in regard to respondents without subjective memory problems and particularly to the respondents diagnosed with dementia.

ALZHEIMER DISEASE

The brain of Alzheimer's patients differs not only with a higher concentration of the β-amyloid but a lower concentrations of DHA and NPD 1 (24, 82). This accounts for the areas responsible for learning abilities and memory. (99) Despite of the fact that most studies confirming the influence of DHA on pathogenesis of Alzheimer's disease were conducted on animals (100, 101), the studies allow to make a conclusion on possible interaction between a daily dose of DHA in ratio and the prevalence of Alzheimer disease (102, 103). In particular there are data that Mediterranean diet can reduce the prevalence of this disease. 104, 105). Anyway these conclusions can be objected. (106, 107, 108) Summing up, it is impossible to state with 100% probability that «the more n 3 FS, the less Alzheimer disease», too many factors should be taken into account while conducting such researches, which makes it to date impossible to single out only the impact of n 3 FS.

The results of intervention studies are more transparent and give evidence that there is no connec-

tion between supplementation of n 3 FS and levels of Alzheimer incidence rate (98) and Alzheimer dementia (109, 103, 110, 111)

Similar situation is observed with Parkinson's disease: there are numerous experiments on mice, which showed that DHA acts neuroptotectively and anti-inflammatory on dopaminergic neurons (112, 113, 114, 115, 116, 117, 118) and in animal experiments with Parkinson's models DHA reduce dopamine-dependent movement disorders. (119,120). However, there is no data confirming protective and therapeutic influence of n3 FS supplementation on the condition of Parkinson's patient. Scientists in general doubt that the result of experiment on mice can be extrapolated on humans and thus explain why most of animal-tested medications do not pass the tests in clinical trials.

Despite the divergence of the regulatory landscape between mouse and human, the pattern of chromatin states (defined by histone modifications) and the large-scale chromatin domains are highly similar between the two species. Half of the genome is well conserved in replication timing (and by proxy, chromatin interaction compartment) with the other half highly plastic both between cell types and between species. It will be interesting to investigate the significance of these conserved and divergent classes of DNA elements at different scales, both with regard to the forces driving evolution and for implications of the use of the laboratory mouse as a model for human disease. (2014) (121)

Most optimistic data on n3 FS influence on neuropsychiatric diseases is provided in regard to EPA supplementation of depression. This is confirmed by large meta-analyses, placebo controlled intervention studies, which report that a daily consumption EPA (200 -2200 mg/d), but not DHA significantly reduce depressive symptoms. (121, 122). At combined administration it is necessary to account that correlation of EPA/ DHA > 60% (121)

Nevertheless, unfortunately there is no evidence of the equally effective impact of LCPUFA supplementation for bipolar disorders (123), borderline disorders, (124), schizophrenia (125), autism (126), children with specific learning disorders (127), or attention deficits and hyperactivity in children (128) (children with ADHS).

Therefore, obviously that the quality of fats is decisive on the possibility of prevention of cardiovascular diseases. On the other hand it refers only to the impact of cod liver oil containing EPA and DHA. There are reliable and available data of prospective and randomised studies as well as meta-analyses, confirming this. Probably it does not spread on other fatty acids, such as shorter chain plant based n-3 PUFAs или n-6 PUFAs. So far accordingly to the latest data Long-chain polyunsaturated fatty acids (LCPUFA) produce important positive effects on a number of most essential functions of the human body but in the first line on the prevention of cardiovascular diseases.

In this connection nutritional supplementation of long-chain polyunsaturated fatty acids (LCPUFA) is recommended or 1-2 portion of fish which according to recommendation of German Nutrition Society should be 80 – 150 grams of low fat fish (salmon, sea perch, cod) and 70 grams of fat fish (herring, mackerels) per week (2,3).

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