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RESEARCH ARTICLE

OMEGA-3 POLYUNSATURATED FATTY ACIDS AND AGE-RELATED DISEASES

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ABSTRACT

The efficacy of Omega-3 PUFA in cardiology is so high that Omega-3 PUFA drugs are added to treatment protocols for patients with cardiovascular diseases in many countries. This group of drugs slows down the processes of oxidative stress and chronic inflammation, thereby making a sizable contribution to the complex treatment of cardiovascular diseases. In addition, Omega-3 PUFA slow down the process of aging and prevent the development of age-related diseases, affecting the rate of telomere shortening.

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INTRODUCTION

When we speak about omega-3 polyunsaturated fatty acids (PUFA), the classical study of Greenland Eskimos should not go unmentioned (Dyerberg *et al*., 1975). Jorn Dyerberg, the Dutch scientist, found out that this population rarely suffered from cardiovascular diseases. The analysis of the composition of plasma esterified fatty acids revealed a higher proportion of palmitic, palmitoleic, and timnodonic acids in Greenland Eskimos, while the linoleic acid concentration in them was below normal values. The author linked the differences in qualitative and quantitative PUFA composition with the Eskimo diet peculiarities, and, in particular, with the consumption of large amounts of ω-3 PUFA-rich fat sea fish. In such a way, omega-3, a special PUFA class, has come in sight of internal medicine specialists.

Classification and functions of omega-3 and omega-6 PUFA

There exist 4 classes of polyunsaturated fatty acids: omega-3, omega-6, omega-7, and omega-9. Fatty acid molecules consist of a polar (acid) center and a non-polar (hydrocarbon) chain. Fatty acids are usually characterized with the use of such parameters, as a hydrocarbon chain length and a number of unsaturated bonds (Δ-bonds) in a molecule, which are designated as "chain length: number of bonds" ratio. The location of the Δ-bond is indicated, if counting from the last methyl group of the hydrocarbon chain. Omega-3 PUFA and omega-6 PUFA are not without interest for internal medicine specialists (Table 1).

The main PUFA functions in human body comprise are the participation in *phospholipid formation for biological membranes in all organs and tissues* (brain, cardiomyocytes, platelets, etc.) and *the synthesis of tissue hormones* – eicosanoids: prostacyclins (PC), prostaglandins (PG), leukotrienes (LT), and thromboxanes (TX). These substances play an active role in the regulation of many body systems' functions, especially, cardiovascular system. Functional properties of the eicosanoids synthesized from omega-3 PUFA and omega-6 PUFa are opposite. The eicosanoids formed from omega-3 PUFA induce *vasodilating* (prostacyclin 3), *antiaggregatory* (thromboxane 3), and *antiinflammatory* (5-series leukotriene) *effects*. The following substances are synthesized from omega-6 PUFA: prostacyclin 2 causes *vasoconstriction*, thromboxane 2 *activates platelet aggregation*

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processes, while leukotriene 4 *augments inflammatory processes*.

Table 1. PUFA nomenclature

Class	Name		Chain	Code
	trivial	systematic		
ω-6	Linolenic acid	Octadecadeinoic	18:2	LA
	γ-linolenic acid	Octadecatrienoic	18:3	GLA
	Dihomo-γ-linolenic acid	Eicosatrienoic	20:3	DGLA
	Arachidonic acid	Eicosatetraenoic	20:4	AA
ω-3	α–linolenic acid	Octadecatrienoic	18:3	ALA
	Timnodonic acid	Eicosapentaenoic	20:5	EPA
		Docosapentaenoic	22:5	DPA
	Cervonic acid	Docosahexaenoic	22:6	DHA

Omega-3 PUFA *normalize blood lipid profile,* decreasing the triglyceride (TG) level by 25-30%, total cholesterol (TC) level by 8-12%, VLDL level by 11-18%, LDL level by 10-15%, and increasing HDL level by up to 10% (Harris, 1997). These effects may be explained by the fact that omega-3 PUFA induce the decrease in TG synthesis in liver, the increase in VLDL elimination rate in liver and peripheral tissues, as well as the increase in excretion of cholesterol catabolism products together with bile acids.

Experiments on animals proved that omega-3 PUFA *slowed down the growth of atherosclerotic plaques*. Besides, the results of clinical trials demonstrate that diets with sufficient quantity of omega-3 PUFA caused *the retardation of progression of angiographically proven coronary atherosclerosis* (Erkkilä *et al*., 2004 and von Schacky *et al*., 1999).

It has to be noted that, in case of sufficient dietary contents, omega-3 PUFA competitively replace AA (omega-6 PUFA) in cell membrane phospholipids. In turn, it brings about such beneficial effects of omega-3 PUFA, as *antiarrhythmic* (prevention of life-threatening arrhythmias and sudden cardiac death) and *antithrombotic* (improvement of antiaggregatory properties of red blood cells and platelets) (Reiffel and McDonald, 2006 and Rosenberg, 2002).

Efficacy of omega-3 PUFA administration in different patient groups

When speaking about omega-3 PUFA impact on blood pressure parameters, it is necessary to understand the mechanisms mediating the effects of omega-3 PUFA. Upon entering human body, ω-3 and ω-6 PUFA go through several metabolic changes. After deodorization and elongation processes, the linolenic acid is transformed into DGLA, which, after deodorization, is transformed into AA. Arachidonic acid is the precursor of 3-series prostaglandins, thromboxanes, leukotrienes, through intermediary of cyclooxygenase and lipoxygenase, respectively. PG and LT participate in the processes of vasoconstriction, platelet aggregation, and the synthesis of inflammatory mediators. α-linolenic acid after similar processes is transformed into EPA. EPA is the precursor of 3-series prostaglandins and 5-series leukotrienes. The physiological effect of the above-mentioned PG is less prominent, as compared to the effect of those formed from AA (2-series), and their impact on vascular tone, platelet aggregation, and inflammation is antagonistic. Through deodorization process, EPA is transformed into DHA. DHA and EPA are the precursors of lipoxins, resolvins (anti-inflammatory placental lipids), and protectins. The above-mentioned compounds have an important role in inflammatory processes and act as endogenous regulators of vascular tone and blood pressure. Dihomo-γ-linolenic acid competes with α-linolenic acid, preventing EPA and DHA synthesis. Thus, the imbalance between ω-3 and ω-6 PUFA impacts peripheral vascular resistance and blood pressure parameters.

Omega-3 PUFA suppress aldosterone secretion. This effect may be related to the change of intracellular signal transduction, the change of plasma viscosity, or the impact on angiotensin-converting enzyme (ACE) activity. It is to be recalled that ACE is the enzyme responsible for the conversion of angiotensin-I into angiotensin-II. One of the effects of angiotensin-II is blood pressure increase. ACE inhibition leads to the decrease in angiotension-II production and aldosterone secretion. Besides, during a study on animals, **ω** -3 PUFA promoted the increase in endothelial nitric oxide (NO) production, which also contributes to vasodilation. (Das, 2004)

Thus, while summing up the effects of ω-3 PUFA on BP parameters, one may highlight the following:

1. Production of 3-series prostaglandins with vasoactive, antiaggregatory, and anti-inflammatory effects;
2. Competitive interaction with ω-6 fatty acids;
3. Suppression of aldosterone secretion;
4. Change of intracellular signal transduction, decrease in plasma viscosity and ACE activity;
5. Increase in endothelial nitric oxide synthesis;
6. Heart rate decrease through the impact on parasympathetic vagal stimulation;
7. Changes in myocyte cell membrane lead to the improvement of left ventricular dyastolic function;
8. Inhibition of the synthesis as to transforming growth factor - beta (TGF-β);
9. Prevention of vascular wall fibrosis and the progression of secondary arterial hypertension

The evidence base that prove the beneficial impact of ω-3 PUFA on BP parameters is quite large. Let us pitch upon the most important and the most significant data, in our opinion.

Patients with normal BP parameters

The results of a clinical trial with the participation162 patients demonstrated that the addition of omega-3 PUFA to diet does not impact the parameters of systolic (SBP) and dyastolic (DBP) blood pressure (Rasmussen *et al*., 2006). 95 males and 67 females aged 30 to 65 years were randomly distributed into 2 groups. Patients in each group kept to a specific diet: diet 1 was rich in monounsaturated fatty acids, while diet 2 was rich in saturated fatty acids. Each group was also additionally randomized as to taking fish oil supplement (3.6 g/day of omega-3 PUFA) or placebo. It was revealed that in patients who kept to diet 1 SBP and DBP level decreased by -2.2% ($p = 0.009$) and -3.8% ($p = 0.0001$), respectively, while changes of SBP and DBP parameters in participants who kept to diet 2

were not statistically significant (-1.0% (p = 0.2084) and -1.1% (p = 0.2116), respectively). At that, DBP parameters were lower in those who kept to diet 1. However, all beneficial effects regarding DBP in patients who kept to the diet rich in monounsaturated fatty acids were lost, if fat consumption was above the average values (>37% energy). Similar results were obtained during a trial with the participation of 37 healthy volunteers: in patients who consumed 1 g/day of omega-3 PUFA no significant BP (both SBP and DBP) changes were observed (Shah *et al*., 2007).

Normotonic patients and patients with essential hypertension

Lawrence J. Appel *et al*. (1993) conducted a meta-analysis of 17 clinical trials, the design of which implied the addition of ω-3 PUFA to patient's diet. Patients with normal BP values participated in 11 trials (n = 728). The addition of ω-3 PUFA to the diet led to significant SBP decrease in two trials, and DBP decrease in one trial. In 6 trials, in which patients with essential hypertension participated (n = 291), significant SBP and DBP decrease was observed in two and four trials, respectively. The qualitative SBP and DBP changes (mm Hg, confidence interval (CI) =95%) was as follows: -1.0 mm Hg (from -2.0 to 0.0 mm Hg) and -0.5 mm Hg (from -1.2 to 0.2 mm Hg) in normotonic patients' trials; -5.5 mm Hg (from -8.1 to -2.9 mm Hg) and -3.5 mm Hg (from -5.0 to -2.1 mm Hg) in hypertonic patients' trials. The doses of ω-3 PUFA were quite high (average dose >3 g/day in 11 trials). The magnitude of BP decrease was the highest in patients with high BP values, but was not related to the administered dose of ω-3 PUFA. Consequently, the authors conclude that the addition of high doses of ω-3 PUFA (exceeding 3 g/day) leads to the clinically significant BP decrease mainly in patients with essential hypertension, as compared to normotonic patients.

Similar results were obtained in another meta-analysis conducted in 2002 by a group of scientists headed by Geleijnse *et al*. (2002). The total of 36 trials conducted during the period from 1999 through 2001 were included into the meta-analysis, and 22 out of them had double blind design. Dose of ω-3 PUFA in most of the trials was pretty high (the average dose was 3.7 g/day). ω-3 PUFA administration led to SBP decrease by 2.1 mm Hg (from 1.0 to 3.2 mm Hg; CI=95%, $p < 0.01$) and DBP decrease by 1.6 mm Hg (from 1.0 to 2.2 mm Hg, CI=95%, $p < 0.01$). More pronounced BP decrease was observed in the patients, who were older than 45 years, in whom essential hypertension (EH, BP ≥ 140/90 mm Hg) was diagnosed. Thus, the authors concluded that the fish oil consumption in the dose of 3.7 g/day or higher may lower the BP, especially in elderly persons and the patients with EH.

Patients with the history of myocardial infarction

According to the results of a multicenter trial, ω-3 PUFA in the dose of 1 g/day are recommended as agents for the secondary prevention of recurrent myocardial infarction (Marchioli *et al*., 2002). The use of the above-mentioned dose of highly purified omega-3 PUFA enables to decrease the risk of sudden death by 45% (Albert *et al*., 2002). Thus, omega-3 PUFA became the honorary "fifth element" of drug therapy of recurrent infarction together with such well-respected drugs as statins, antithrombotic drugs, ACE inhibitors, and b-blockers.

Patients with diabetes mellitus

British scientists conducted a meta-analysis of 12 randomized clinical trials performed during the period from 1966 through 2006, in which the impact of omega-3 PUFA on hematological and thrombogenic risk markers in patients with dyslipidemia and type 2 diabetes mellitus was evaluated (Hartweg *et al*., 2007). The changes of such parameters as C-reactive protein, IL-6, TNF-α, platelet function, fibrinogen, factor VII, von Willebrand factor, endothelial function, etc., were evaluated, but, for the purposes of this article, let us discuss BP changes in this population. In comparison with placebo, omega-3 PUFA mostly impacted DBP value change (from 0.0 mm Hg to -3.6 mm Hg, mean -1.8 mm Hg, CI = 95%, p = 0.05). . No significant changes of SBP level, fibrinogen level, or heart rate (HR) were observed.

The results of another meta-analysis of 24 clinical trials demonstrated different results. The group of scientists headed by Hartweg *et al*. (2009) traced the changes of lipid profile, glycemic and hematological risk factors in patients with type 2 diabetes mellitus against the background of ω-3 PUFA supplement addition to their diet. The study participants administered 2.4 g/day of omega-3 PUFA for 24 weeks. In comparison with placebo, in the group of patients, who administered omega-3 PUFA, triglyceride level decreased by 7% (mean change – 0.17 mmol/l, 24 clinical trials (CT), 1530 patients), fibrinogen level decreased by 10% (mean change – 0.96 mcmol/l, 3 CT, 159 patients), collagen level decreased by 21% (mean change – 10.55%, 2 CT, 64 patients), while HDL level increased by 3% (mean change - 0.08 mmol/l, 21 CT, 1104 patients). The levels of glycemia, insulinemia, inflammatory biomarkers were not significantly affected by the administration of ω-3 PUFa. It has to be noted that, when ω-3 PUFA was supplemented, BP (both SBP and DBP) level change was not statistically significant (SBP: -0.78 mm Hg, p=0.44; DBP: -0.79 mm Hg, p=0.18).

Infancy

Quite often, the question that nhas to be answered by clinicians is as follows: when to administer the drugs containing fish oil? The correctness of various hypotheses is the subject for discussions among world's leading scientists. For the purposes of this article, we would like to draw your attention to an interesting randomized trial (in our opinion), which is the first one of its kind (Damsgaard *et al*., 2006). One of the objectives stated by the trial authors was to evaluate the impact, that omega-3 PUFA have on BP in infants. The results of the previous animal studies showed that the diet quality and type early in the life may have a long-term impact on BP, cholesterol metabolism, and the features of atherosclerosis course (Lucas *et al*., 1999). Breastfeeding is associated with good BP parameters (Owen *et al*., 2002 and Singhal *et al*., 2001). Breast milk is a source of omega-3 PUFA, (Lauritzen *et al*., 2001) and the results of many studies show that omega-3 PUFA administration in the early life is associated with lower BP values in adulthood (Armitage *et al*., 2003 and Forsyth *et al*., 2003). 94 infants (aged 9 months) were included in the study. Inclusion criteria were as follows: birth at ≥ 37 week of gestation; body mass at birth > 2,500 g; Apgar score of

≥ 7 points at the 5th minute of assessment; absence of any serious complications in labor and during embryo life; absence of any chronic diseases. The study participants were divided into two groups: children in the first group (n=49) did not take fish oil, and those in the second group (n=45) took 5 ml of fish oil daily. In turn, 22 patients from the first group ate standard infant formulas, while 27 patients drank cow milk. Participants from the second group were divided into the following sub-groups: fish oil + standard infant formula (n=26) and fish oil + cow milk. The patients were followed up for 3 months (from 9th to 12th months of a child's life). According to the results of the trial, regardless of fish oil intake, DBP and mean BP (the arithmetic mean of SBP and DBP parameters) values did not differ significantly between groups. The situation was the other way round for SBP parameters: infants that took fish oil had lower SBP level (-5.6 ± 3.1 mm Hg, p=0.06), as compared to infants whose diet was not enhanced with fish oil (2.4 ± 2.8 mm Hg, p=0.43). No significant BP changes were observed in the children who drank cow milk (Table 2).

EPA and DHA concentration in red blood cells (the proportion of the total PUFA amount) in the group of children who took fish oil increased from 0.6 ± 0.1 to 3.2 ± 0.2%, and from 5.5 ± 0.3 to 7.5 ± 0.2 %, respectively (p < 0,001). Meanwhile, LA and AA concentration in red blood cells decreased from 10.7 ± 0.2 to 9.2 ± 0.2% (p < 0.001), and from 16.3 ± 0.3 to 13.7 ± 0.3% (p < 0.05), respectively (Figure 1). No such changes were observed in the group of children who did not take fish oil.

Patients on hemodialysis

Kidney is one of the target organs for hypertonic process. Kidney function disorders developing in essential hypertension are more often the consequence, rather than the cause of the disease. Besides, such disorders may promote the progression of disease. In present day nephrosclerosis, being the most frequent endpoint of high BP impact on kidneys, is responsible for 10 to 20% of all new cases of the need for dialysis.

Table 2. Impact of omega-3 PUFA on BP parameters (Damsgaard *et al.*, 2006)

Parameter	Group of children who did not take fish oil	Group of children who took fish oil
Systolic BP *(mm Hg)*		
9th month (p=0.27)	106.6 ± 2.0	109.9 ± 2.2
12th month (p=0.05)	108.8 ± 1.7	104.1 ± 1.7
Dyastolic BP *(mm Hg)*		
9th month (p=0.65)	63.7 ± 1.7	64.9 ± 1.9
12th month (p=0.43)	63.4 ± 1.8	61.4 ± 1.8
Mean blood pressure *(mm Hg)*		
9th month (p=0.76)	79.6 ± 1.5	80.3 ± 1.8
12th month (p=0.91)	79.1 ± 1.5	78.8 ± 1.6

Special attention should be paid to the parameters of omega-3 PUFA concentration in red blood cells of the patients under trial. As it was mentioned above, the main effects of this drug class are implemented through those omega-3 PUFA that comprise phospholipids of biological membranes. Omega-3 index of red blood cells is the parameter representing the sum of eicosapentaenoic and docosahexaenoic PUFA percentage in the red blood cell membrane (Harris and von Schacky, 2004). It was proven that this parameter is of high value as a predictor of various cardiovascular complications, including sudden cardiac death (<4% - high risk of cardiovascular diseases; 4.1-7.9% - moderate risk; >8% - low risk).

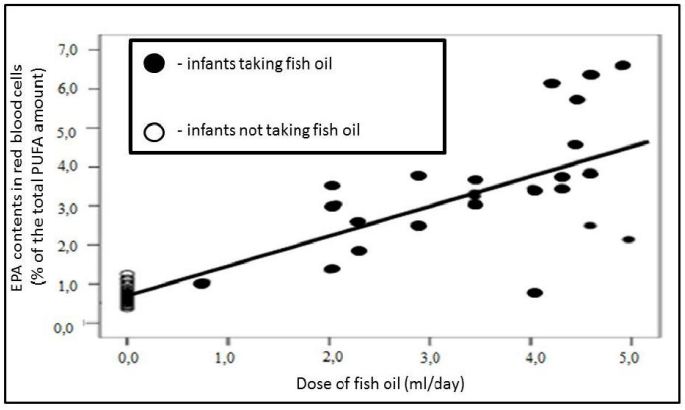

Figure 1. EPA percentage in red blood cells of children at the 12th month of life (r=0.86, p<0.001, n=53) (Damsgaard *et al.*, 2006)

As of December 31, 2011, 28 548 patients in Russia with terminal renal failure received renal replacement therapy (RRT). The rate of patient number increase in 2011 with regard to the previous year was 8.7%, which is less than the mean value for years 2006 through 2010 (9.8%), though the rate of patient number increase in Russia still exceeds the mean global statistics (Bikbov, 2014), which is typical for the countries with insufficient RRT availability. Beyond dispute, treatment of high BP in this category of patients has some specifics, but in the context of this article we will discuss just the efficacy of omega-3 PUFA in BP correction in these patients.

Vernaglione *et al*. (2008) conducted a trial, where changes of BP parameters in patients on hemodialysis (n=24) were analyzed. For this purpose, the trial participants were offered to keep to a specific diet (3 steps): in the first 4 months, the diet was supplemented with olive oil (2 g/day), in the second 4 months - with omega-3 PUFA (2 g/day), and in the next 4 months, with olive oil (2 g/day) again. According to the results, SBP and DBP values were significantly lower (p<0.05) at the end of the second trial step. SBP decreased from 131 ± 17.8 mm Hg at the end of the first step to 122 mm Hg in the second step, and increased again to 129 ± 13.2 mm Hg. Similar changes were also observed for DBP: 83 ± 16.3 mm Hg at the end of the first step, 71 ± 14.8 mm Hg in the second step, and 79 ± 6.5 mm Hg in the third trial step. Thus, the authors state that drugs contatining omega-3 PUFA may be used for treatment of patients on hemodialysis to achieve target BP values.

Aging and essential hypertension

Free radical processes play a very important role in biosynthesis of such biologically active substances as prostaglandins, leukotrienes, prostacyclins, and thromboxanes. The disorder of free radical reactions' regulation is accompanied by uncontrolled non-enzyme oxidation of polyenoic lipids and carbohydrate autooxidation, as well as the oxidative damage of nucleic acids and proteins, which leads to the emergence of the so-called oxidative stress (OS); OS is characterized by the accumulation of primary (organic hydroperoxides) and secondary (carbonyl compounds) highly toxic products of free radical oxidation in blood and tissues, increased generation of reactive oxygen species (ROS) (superoxide anion radical, hydrogen peroxide), and/or suppression of activity of antioxidant enzymes scavenging ROS (superoxide dismutase, glutathione peroxidase - GSH-Px) (Lanzin *et al*., 2013).

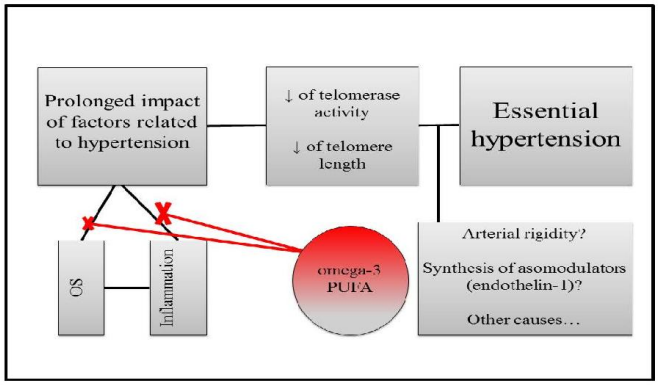

Figure 2. Hypothetic model of telomere and telomerase changes at different stages of essential hypertension development, and the possible impact of omega-3 PUFA (Drapkina and Shepel, 2013)

It should be noted that oxidative damages to deoxyribonucleic acid (DNA) primarily occur in telomeric DNA areas. Telomeres are the terminal areas of linear chromosome DNA consisting of multiple repeating nucleotide sequences and specifically bound proteins (Drapkina and Shepel, 2013; Ivashkin, 2015 and Drapkina and Shepel, 2015). Main telomere functions are as follows: *mechanical* (participate in chromosome fixation to nuclear matrix), *stabilizing* (prevent the under-replication of genetically significant DNA areas, stabilize the ends of the torn chromosomes), *impact on gene expression, and "counting" function* (telomeres act as a "device" that determines the number of divisions that a normal cell is able to perform in the absence of telomerase) (Drapkina and Shepel, 2014). As a rule, oxidate stress is associated with chronic inflammation (Finch and Crimmins, 2004). The mentioned processes, when they act for prolonged periods, inhibit the activity of telomerase, the enzyme mainly responsible for telomere reparation. This, in turn, leads to telomere shortening (Xu *et al*., 2000; Breitschopf *et al*., 2001 and Kurz *et al*., 2004). The above-mentioned processes also form the basis for the development of essential hypertension.

Omega-3 PUFA and telomeres

The results of multiple clinical trials demonstrate that the length of telomeres is less in patients with EH, as compared to patients without EH (Drapkina and Shepel, 2013, 2015). Besides, there is evidence that in hypertonic patients the activity of telomerase in endothelial cells-precursors is decreased, which contributes to the lesser telomere length in those cells (Imanishi *et al*., 2005). All the above-described data assign new tasks for scientists and clinicians in terms of searching for new methods of EH prevention and treatment (Figure 2).

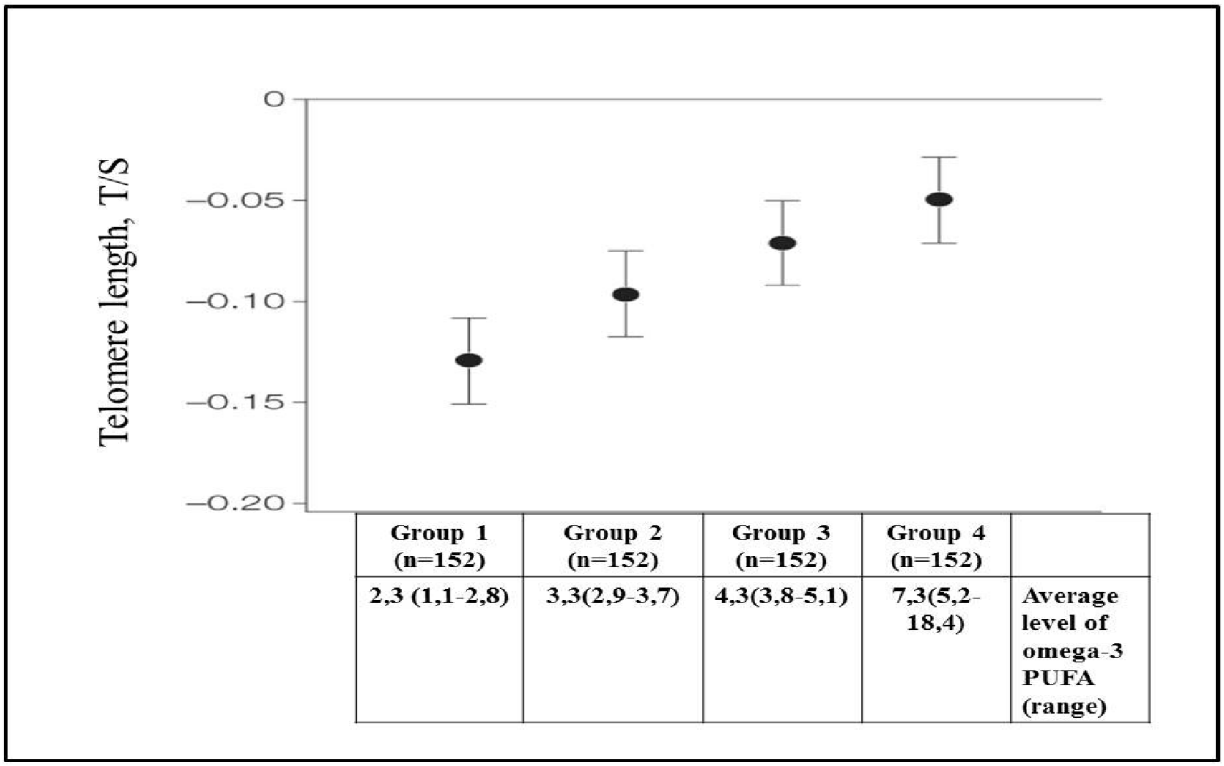

Figure 3. Connection between telomere length and mean plasma level of omega-3 fatty acids (Farzaneh-Far *et al*., 2010)

Ramin Farzaneh – Far *et al*. evaluated the impact of omega-3 PUFA on the telomere length in patients with stable ischemic heart disease (Farzaneh-Far *et al*., 2010). For the above-mentioned purpose, 608 patients were included into the trial. It lasted for 5 years. In the beginning and in the end of the trial, telomere length was measured in patients (relative telomere length was evaluated using the T/S parameter, which was calculated as the ratio of the number of telomere repeated copies to the number of albumin gene copies). Besides, the plasma level of omega-3 fatty acids (DHA and EPA) was measured in patients, and its connection with telomere length was evaluated. The results of the trial are presented in Figure 3. The group of patients, in which mean blood DHA + EPA level was 2.3%, had the highest rate of telomere shortening (0.13 T/S (0.09–0.17), CI=95%, $p<0.001$), while the lowest rate of telomere shortening (0.05 T/S (0.02–0.08), CI=95%, $p<0.001$) was observed in patients with high blood DHA + EPA level (7.3%). Blood pressure parameters in the 4th group were significantly lower, as compared to the 1st group patients (129/74 mm Hg and 134/74 mm Hg, respectively). The authors of the trial suggest that one of the possible explanations for the impact of omega-3 PUFA on the rate of telomere length shortening lies in the oxidative stress: reactive oxygen species selectively interact with GGG-areas of telomeres and contribute to the increase in the rate of telomere shortening in mitosis.

Despite the fact that EPA and DHA are more vulnerable to oxidation processes than omega-6 PUFA (AA in particular), the addition of omega-3 PUFA to diet is associated with the low level of F2-isoprostans (standard indicator of systemic oxidative stress), as well as with the higher level of antioxidative enzymes (catalase, superoxide dismutase). The second potential mechanism that can help to explain the connection of omega-3 fatty acids and the rate of telomere shortening is the activity of telomerase enzyme. Up until recently, it has been thought that embryonic, stem and cancer cells had high telomerase activity during the whole life, while there is no telomerase activity in somatic cells. Nevertheless, the results of the studies demonstrate that low telomerase activity is observed in T-lymphocytes. It was found out that high telomerase activity was observed in the sub-population of thymocytes, and its moderate activity was seen in T-lymphocytes of tonsils.

In peripheral blood, the level of T-lymphocyte telomerase activity varied from low to indeterminable level (Weng *et al*., 1996). In healthy patients, the daily intake of 3 g of omega-3 PUFA is associated with significant increase of telomerase activity (Ornish *et al*., 2008). At the same time, in patients with colorectal adenocarcinoma, who took EPA and DHA, telomerase activity was lower than in patients who did not take omega-3 PUFA (Eitsuka *et al*., 2005). Analyzing the above-mentioned observations, one may suggest that omega-3 fatty acids can have a two-fold impact on telomerases, depending on cells context: they increase the telomerase activity in healthy tissues and suppress its activity in cancer cells. In other American study, the authors also set a task to find connection between oxidative stress, white blood cell telomere length and omega-3 PUFA intake. For the above-mentioned purpose, 106 males and females were included into the trial, aged in the range from 40 to 85 years. The patients were divided into 3 groups: the 1st group received 2.5 g/day of omega-3 PUFA, the 2nd group received 1.25 g/day of omega-3 PUFA, and the 3rd group received placebo. The trial lasted for 4 months. In patients who did not take supplements with omega-3 PUFA, the level of indicators of systemic oxidative stress (F2-isoprostans) increased by 8% (0.073 ng/ml, $p=0.02$), while in the 1st and 2nd groups the level of F2-isoprostans decreased by 8% and 9%, respectively (-0.094, $p=0.04$ and -0.086, $p=0.99$). Telomerase activity in the first group increased by 54%, in the second group - by 53%, and only by 39% in the placebo group. Telomere length in the 1st and 2nd groups increased by 50 and 21 base pairs, respectively, while telomere length in the placebo group decreased by 43 base pairs. Thus, the primary data on telomere length in three groups did not differ significantly. It is known that in each human PUFA are absorbed and metabolized individually.

Besides, the medication adherence of the patients is also an ongoing challenge. For the above-mentioned purpose, the ω-6:ω-3 PUFA ratio was calculated, and the evaluation of its connection with telomere length was conducted. The decrease of ω-6:ω-3 ratio is associated with the increase in telomere length by 20 nucleotide pairs ($p=0.02$). Taking into account the inclusion of the most frequent fatty acids of each class, the ω-6:ω-3 ratio may be presented as AA:(EPA+DHA). The decrease in AA: (EPA+DHA) ratio is associated with the increase in telomere length by 35 nucleotide pairs ($p=0.08$). Similarly, if the ω-6:ω-3 ratio is presented as AA:(EPA+DHA+DPA), the ratio increase by 1 unit correlated with the telomere increase by 22 nucleotide pairs ($p=0.07$). Thus, despite the fact that changes of telomerase activity and telomere length in omega-3 PUFA intake were insignificant, the data analysis adjusted for the ω-6:ω-3 ratio in plasma brought in some corrections: telomere length increases with the decrease in ω-6:ω-3 ratio. To sum it up, low ω-6:ω-3 ratio may have an impact on cell aging.

Conclusion

The efficacy of omega-3 PUFA use in cardiology is so high that in many countries omega-3 PUFA drugs are added to treatment protocols for patients with cardiovascular diseases together with aspirin, warfarin and other drugs (Belenkov *et al*., 2011). These drugs are especially important in abandoning the traditional dietary forms that included the intake of large amounts of fresh fish. Omega-3 PUFA drugs have a good tolerability and practically no side effects. The patients with the history of cardiovascular diseases are recommended to eat fat fish species twice a week, or add ALA-rich food (flaxseed, rapeseed, soyabean, walnut oils) to their diet. Patients with essential hypertension are recommended to take 1.0 g/day of EPA+DHA in the form of fish oil or biologically active supplements (BAS) as an addition to basic hypotensive treatment (ESC/ESH, 2013). Doses of omega-3 PUFA mentioned above, apart from the beneficial effect on the course of essential hypertension, also have a protective effect at the molecular-genetic level, contributing to slowing down the rate of telomere shortening. The decrease in the rate of telomere shortening, in its turn, contributes to the slowdown of the process of ageing and the development of age-related diseases.

Conflict of interests

All authors declare that there exists no potential conflict of interests that might need to be disclosed in this article.

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