THE EFFECT OF OMEGA-3 POLYUNSATURATED FATTY ACIDS ON N-TERMINAL PRO-BRAIN NATRIURETIC PEPTIDE AND LIPIDS CONCENTRATION IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND CARDIOVASCULAR AUTONOMIC NEUROPATHY

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Abstract

Background and Aims: Cardiac autonomic neuropathy (CAN) in type 2 diabetes mellitus (T2DM) is one of the independent risk factor for cardiovascular mortality. The aim of the study was to analyze the effect of long-chain ω-3 polyunsaturated fatty acids (ω-3 PUFA) on the levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) and on some lipid profile parameters in patients with T2DM and CAN. Material and Methods: 36 patients with T2DM and verified CAN were divided into 2 groups. The first group received traditional hypoglycemic therapy (n = 15, control) for three months; patients in group 2 (n = 21) received in addition 1 g/day of the long-chain ω-3 PUFA for three months. Results: Prescription of the ω-3 PUFA to the patients with T2DM and CAN was accompanied by a statistically significant decrease of NT-proBNP level and led to significantly positive changes in the high density lipoprotein cholesterol and triglycerides levels in the blood. Conclusions: Obtained results suggest that the efficacy of ω-3 PUFA is the result of a direct effect of the pharmacological agent on the investigated indexes.

key words: type 2 diabetes mellitus, cardiovascular autonomic neuropathy, long-chain omega-3 polyunsaturated fatty acids, N-terminal pro-brain natriuretic peptide, lipids.

Background and aims

Cardiac autonomic neuropathy (CAN) in type 2 diabetes mellitus (T2DM), which is characterized by lesions of nerve fibers in parasympathetic and sympathetic nervous system, is one of the leading causes of heart arrhythmias and an independent risk factor for cardiovascular mortality in these patients [1,2]. Therefore, the problem of effective treatment of CAN is particularly relevant. Pathogenetic treatment of CAN includes: balanced diet and physical activity; optimizing of glycemic control; treatment of dyslipoproteinemia (DLP); correction of metabolic abnormalities in the myocardium; prevention and treatment of thrombosis; use of aldose reductase inhibitors; γ-linolenic acid, acetyl-L-carnitine, antioxidants, first of all α-lipoic acid, use of long-chain ω-3 and ω-6 polyunsaturated fatty acids (ω-3 and ω-6 PUFA), vasodilators, fat-soluble vitamin B1, aminoguanidine; substitutive therapy of growth factors and others [1,3].
Raised plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) predict cardiovascular mortality in general population, is typically increased in patients with left ventricular dysfunction and is associated with coronary artery disease and myocardial ischemia [4,5]. In patients with T2DM, elevated circulating NT-proBNP is a strong predictor of the excess overall and cardiovascular mortality and this predictor status being independent of conventional cardiovascular risk factors [6]. It is known that patients with T2DM often associate DLP, which is characterized by increased triglycerides (TG) concentration and decreased high density lipoproteins cholesterol (HDL-cholesterol) level. It was suggested that the use of medicines which contain ω-3 and ω-6 PUFA could be accompanied by positive changes in lipid metabolism [3,7]. However, research regarding the effect of ω-3 and ω-6 PUFA in diabetic patients without diagnosed coronary heart disease (CHD) (despite evidences that T2DM is an equivalent of CHD) are scarce, and the results do not confirm their effectiveness [8,9].

The objective of our study was to analyze the effect of long-chain ω-3 PUFA on the levels of NT-proBNP and on some lipid profile parameters in patients with T2DM and CAN.

Material and methods

A total of 36 patients with T2DM and confirmed CAN were included in the study. The work was done according to the principles of the Declaration of Helsinki (2004) and all subjects signed an informed consent prior their inclusion in the study.

Patients were aged between 50-59 years, had disease duration between 1-6 years and mean HbA1c level of 7.1 ± 0.5 %. CAN was diagnosed according to previously proposed criteria [10,11]. Patients with T2DM and CAN were divided into 2 groups. First group received traditional hypoglycemic therapy (n = 15, control group) for three months; patients in group 2 (n = 21), received in addition to standard treatment 1 capsule/day of the ω-3 PUFA for three months. The capsule contains 1 g, including ~90 % ω-3 PUFA, mainly eicosapentaenoic (EPA) and docosahexaenoic acids (DHA).

The concentration of glucose in the blood was determined by the glucose oxidase method while HbA1c was assessed using a highly sensitive method of ion-exchange liquid chromatography with a D-10 analyzer and BIO-RAD reagents (USA). Determination of NT-proBNP was performed using commercial kits from Biomedica (Austria) and an ELISA analysis technique. Lipid metabolism was assessed by the concentration of total cholesterol, TG, HDL cholesterol and low density lipoprotein cholesterol (LDL cholesterol). The lipid fractions were determined using HUMAN reagents (Germany) for the analyzer HUMANLAYZER 2000.

Statistical analysis

Statistical analysis was based on the variational method using statistical parametric t-test, nonparametric Wilcoxon t-test and Fisher's Pearson correlation coefficient. All tests were performed using the ANOVA (MicroCal Origin v. 8.0) software. Statistical significance was set at p < 0.05.

Results

We found that the HbA1c of patients with T2DM and CAN was not statistically significant influenced by the treatment (p > 0.05).

Treatment with the drug containing ω-3 PUFA in patients with T2DM and CAN (group 2) led to a significant increase of the HDL cholesterol level [+7.1 ± 0.5 % (p < 0.05)] and
reduction of TG [-35.4 ± 2.6%, (p < 0.05)]. The treatment also led to a significant decrease of the NT-proBNP level [-6.8±1.1% (p < 0.05)] compared to the control group.

Changes of NT-proBNP and lipid metabolism parameters in patients with T2DM and CAN after 3-months of ω-3 PUFA therapy are given in Table 1.

Table 1. Changes of the NT-proBNP level and lipid metabolism parameters in patients with T2DM and CAN after 3-months of ω-3 PUFA therapy (Δ %, Mean±SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients with T2DM and CAN (n = 36)</th>
<th>Control (n = 15)</th>
<th>ω-3 PUFA (n = 21)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>group 1</td>
<td>group 2</td>
<td></td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>-3.0 ± 1.1</td>
<td>-6.8 ± 1.1</td>
<td>p &lt; 0.05</td>
<td></td>
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<tr>
<td>LDL cholesterol</td>
<td>-8.3 ± 1.4</td>
<td>-12.8 ± 1.9</td>
<td>p &gt; 0.05</td>
<td></td>
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<tr>
<td>HDL cholesterol</td>
<td>+4.1 ± 1.0</td>
<td>+7.1 ± 0.5</td>
<td>p &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td>-8.3 ± 1.2</td>
<td>-35.4 ± 2.6</td>
<td>p &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>-6.7 ± 1.0</td>
<td>-8.2 ± 1.1s</td>
<td>p &gt; 0.05</td>
<td></td>
</tr>
</tbody>
</table>

Note. The results are presented as % change from baseline; differences were statistically significant at the level of p < 0.05 compared with the control group.

**Discussions**

Analysis of experimental and clinical studies proves that ω-3 PUFA inhibit the absorption of cholesterol in the intestine and its synthesis in the liver, lead to increased clearance of lipoproteins in the blood, prevent the development of insulin resistance (IR) in experimental diabetes, raise levels of glucose transporters GLUT4 mitochondrial RNA in skeletal muscles, have a positive effect on the age related decrease of blood flow in the brain and improve utilization of glucose in hypertensive rats under stress [7,12,13]. However, there is no influence on the development of obesity. Omega-3 PUFA decrease level of blood pressure, dose-dependently prevent the development of diabetes, IR, improve the sensitivity of platelets to ADP and collagen, contribute to positive changes in the parameters of coagulation, endothelial cells migration, inhibits the proliferation of smooth muscle cells [7,14]. However, the results of the ORIGIN trial showed that administration of 1 g ω-3 PUFA did not reduce the rate of death from cardiovascular causes or their outcomes during a period of 6 years in patients with dysglycemia and additional cardiovascular risk factors. In this trial, the dose of ω-3 PUFA was not chosen on the basis of any estimate of its effect on TG levels, nevertheless, a significant reduction in the TG level was shown [15]. However, this study did not investigate the effect on CAN and it was decided to continue the study for a few years.

We previously reported that the use of "Omacor®”, which contains in one capsule ~90% ω-3 PUFA, mainly EPA and DHA, in the treatment of patients with T2DM and CAN improved the general condition of the patients [12]. Thus, prescription of ω-3 PUFA contributed to a significant decrease of mean diastolic blood pressure (DBP), time index of diastolic hypertension, diastolic hypertension area index and variability of DBP during the day and night hours and was accompanied by a tendency to a low pulse pressure [12].

The influence of ω-3 PUFA on the dynamics of metabolism is probably due to their effects on IR, glucose homeostasis and lipid metabolism (improvement of the lipid profile in patients with T2DM and DLP). In addition, ω-3 PUFA moderately reduce BP, improve endothelial function, reduce proinflammatory status and improve antioxidant protection [8,13,16].
The combination of the positive influences of ω-3 PUFA on NT-proBNP, lipid profile and their moderate hypotensive effects [17] suggests the feasibility of their use in the complex treatment of patients with T2DM and CAN. Further investigations aimed to establish the influence of ω-3 PUFA on dynamics of independent cardiovascular tests, daily monitoring of ECG, daily monitoring of BP, arterial wall stiffness parameters in patients with T2DM and CAN are necessary.

Conclusions

Prescription of the ω-3 PUFA in patients with T2DM and CAN was accompanied by a statistically significant decrease of NT-proBNP levels in the blood. It also contributed to significantly positive changes in the concentration of HDL cholesterol and TG compared with the control group. Our results suggest that the efficacy of ω-3 PUFA is not associated with improved glycemic control of T2DM in patients with CAN, but is rather the result of a direct effect of the pharmacological agent on the investigated metabolic indexes.

Conflicts of interest: The authors have no conflicts of interest to declare in relation to this article.

REFERENCES


