http://rjdnmd.org
Rom J Diabetes Nutr Metab Dis. **25**(4):363-368
doi: 10.2478/rjdnmd-2018-0043

OMEGA-3 POLYUNSATURATED FATTY ACIDS IMPROVED ARTERIAL STIFFNESS PARAMETERS IN TYPE 2 DIABETIC PATIENTS WITH CARDIAC AUTONOMIC NEUROPATHY

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received: July 04, 2018 *accepted*: November 29, 2018
available online: December 25, 2018

Abstract

Background and Aims: *Diabetic cardiac autonomic neuropathy (DCAN) in type 2 diabetes (T2D) is among the strongest and independent risk markers for future global and cardiac mortality.* ***Material and Methods:*** *Thirty-six patients suffering from T2D and confirmed DCAN were enrolled in this investigation. Depending on the prescribed therapy, patients were allocated into two groups: group 1 was comprised of 15 patients to whom standard hypoglycemic treatment was prescribed (control group), the second received standard hypoglycemic treatment and omega-3 polyunsaturated fatty acids (ω-3 PUFAs, n = 21). The duration of the study was three month.* ***Results:*** *In subjects with T2D and DCAN prescription of ω-3 PUFAs was associated with a significant decrease of aorta augmentation index (AIxao), pulse wave velocity (PWV) during the active period of the day and decrease of AIxao, brachial augmentation index and PWV during the passive period of the day compared with the control group. Therefore, three month of ω-3 PUFAs supplementation to patients with confirmed DCAN and T2D promotes to improvement of arterial stiffness indices.* ***Conclusions:*** *In patients with T2D and CAN treatment with ω-3 PUFAs improved arterial stiffness parameters. The effectiveness of ω-3 PUFAs is not connected with optimization of glycemic control, but is rather the result of a direct drug action on the studied parameters.*

key words: *type 2 diabetes, diabetic cardiac autonomic neuropathy, arterial stiffness parameters, omega-3 polyunsaturated fatty acids*

Background and aims

Coronary artery disease (CAD) due to early atherosclerosis is often diagnosed among the majority of type 2 diabetes (T2D) patients.

The term “diabetic heart” is associated with early affection of coronary vessels, development of arterial sclerotic disease, diabetic cardiomyopathy and diabetic cardiac autonomic neuropathy (DCAN) among midlife and elderly persons [1,2]. DCAN is one of the common condition that lead to development of cardiac rhythm disturbances and an independent risk marker for future global and cardiac mortality [3,4]. At this time, there is no proven effective treatment of DCAN [3-5].

Aging and atherosclerosis are the leading causes of the arterial stiffening due to vascular

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elasticity loss. Arterial stiffening depends from the distribution of extracellular proteins along the arterial wall, its balance and structural properties of the arterial wall [6,7]. Arterial stiffening occurs as a consequence of biological aging and is closely associated with several conditions leading to increased cardiac risk such as hypertension, obesity, smoking and T2D. Pulse wave velocity (PWV) is an evaluation criterion of central stiffness measurement and its interpretation constitutes a diagnostic non-invasive procedure, that can be utilised to evaluate blood flow in radial, femoral or carotid artery using certain devices [8-10].

Meta-analysis of randomized clinical trials provides compelling evidence that prescription of omega-3 polyunsaturated fatty acids (ω-3 PUFAs) offers a scientifically supported means of reducing arterial stiffness [11-13]. However, investigations regarding the effectiveness of ω-3 and ω-6 PUFA in terms of diabetes without verified CAD (regardless of numeral data that T2D is valued as analogue to CAD) are lacking, and its results do not validate their efficacy [14,15].

In this study we evaluated the effect of long-chain ω-3 PUFAs on the arterial stiffness indices in T2D patients with confirmed DCAN.

Material and methods

Thirty-six patients suffering from T2D and confirmed DCAN were enrolled to the investigation. The research was conducted in accordance with the principles of the Declaration of Helsinki (2004). All patients were informed orally about the study and prior their inclusion in the study have signed the corresponding informed consent.

The study population included patients aged between 50 and 59 years, with median glycated hemoglobin A_{1c} (HbA_{1c}) level of 7.1 ± 0.5% and duration of T2D between 1 and 6 years. DCAN was diagnosed according to [16,4]. Cardiovascular autonomic reflex tests (CARTs) are the "gold" standard clinical tests for DCAN. In accordance with DCAN subcommittee in the Toronto Diabetic Neuropathy Consensus Panel, one abnormal CART result (between the seven tests (five CARTs, time- and frequency-domain heart rate variability tests) is sufficient for DCAN diagnosis, two or three abnormal results confirm DCAN manifestation; and development of orthostatic hypotension indicate severe DCAN [16,4].

Depending on the prescribed therapy, patients were allocated into two groups: group 1 was comprised of 15 patients to whom standard hypoglycemic treatment was prescribed (control group), the second (treatment group, n = 21) received standard hypoglycemic treatment and 1 capsule/day of the ω-3 PUFAs, which contains 1g, including ~90% ω-3 PUFAs, mainly docosahexaenoic and eicosapentaenoic acids, in addition to standard treatment. The study duration was three months.

The highly sensitive method of ion-exchange liquid chromatography with BIO-RAD reagents and D-10 analyzer (USA) was used to perform measurements of HbA_{1c} level, while glucose level was determined by glucose oxidase method. Electrocardiography (ECG) results were analyzed using a 12-channel electrocardiograph "UCARD-200" (UTAS, Ukraine) and Holter-ECG [ECG "The EC-3H" (Labtech, Hungary)]. Determination of intracardiac hemodynamics parameters and structure-functional state of the myocardium was assessed using the "Siemens Sonoline Versa Plus" (Germany). Artery stiffness parameters were assessed using the device TensioMed™ Arteriograph [monitor BP "ABPM-04" ("Meditech", Hungary)]. We investigated following parameters: aorta augmentation index (AIxao), brachial augmentation index (AIxbr) and PWV. The

optimal values: PWV less than 7 m/s, AIxbr more than -30%; normal values: PWV from 7 m/s to 10 m/s, AIxbr from -30% to -10%; elevated values: PWV from 10 m/s to 12 m/s, AIxbr from -10% to 10%; pathological values: PWV more than 12 m/s and AIxbr more than 10% [17,6].

Statistical analysis

Statistical analysis: parametric t-test, Fisher's Pearson correlation coefficient and nonparametric Wilcoxon t-test were used. One-way ANOVA (MicroCal Origin v. 8.0) was used to compare means of the groups. P value was considered significant at < 0.05.

Results

The level of HbA_{1c} in patients with confirmed DCAN and T2D did not change significantly after treatment (p > 0.05).

Changes of arterial stiffness indices among persons with confirmed DCAN and T2D after three months of ω-3 PUFAs prescription are presented in Tables 1 and 2.

Table 1. Changes of the arterial stiffness indices during the active period of day in patients with confirmed DCAN and T2D after three months of ω-3 PUFAs treatment (Δ%, Mean ± SEM)

Parameter	Patients with confirmed DCAN and T2D (n = 36)				
	Groups	Before therapy	After therapy	% change	p
AIxao (%)	Control (n = 15)	30.5 ± 2.09	28.4 ± 1.89	-5.0 % ± 5.03 %	> 0.05
	ω-3 PUFAs (n = 21)	32.0 ± 1.32	26.4 ± 1.12	-16.2 % ± 3.12 %	< 0.01
AIxbr (%)	Control (n = 15)	-11.01 ± 3.7	-12.2 ± 3.32	-20.9 % ± 13.7 %	> 0.05
	ω-3 PUFAs (n = 21)	-9.8 ± 2.76	-14.3 ± 2.84	-42.8 % ± 9.0 %	> 0.05
PWV (m/s)	Control (n = 15)	10.0 ± 0.45	9.3 ± 0.42	-6.4 % ± 2.45 %	> 0.05
	ω-3 PUFAs (n = 21)	11.0 ± 0.35	9.7 ± 0.39	-11.6 % ± 2.09 %	< 0.05

Results in the table are presented as % change from baseline (Δ%, Mean ± SEM) and absolute values; DCAN: diabetic cardiac autonomic neuropathy; T2D: type 2 diabetes; AIxao: aorta augmentation index; PWV: pulse wave velocity; AIxbr: brachial augmentation index; SEM: standard error of the mean.

Table 2. Changes of the arterial stiffness indices during the passive period of day in patients with confirmed DCAN and T2D after three months of ω-3 PUFAs treatment (Δ%, Mean ± SEM)

Parameter	Patients with confirmed DCAN and T2D (n = 36)				
	Groups	Before therapy	After therapy	% change	p
AIxao (%)	Control (n = 15)	33.3 ± 1.95	30.1 ± 1.39	-6.1% ± 4.14%	> 0.05
	ω-3 PUFAs (n = 21)	36.6 ± 1.65	31.7 ± 1.23	-11.2% ± 4.2%	< 0.05
AIxbr (%)	Control (n = 15)	-4.5 ± 3.15	-6.5 ± 2.71	-17.7% ± 17.5%	> 0.05
	ω-3 PUFAs (n = 21)	-1.6 ± 2.79	-10.4 ± 3.23	-98.0% ± 18.1%	< 0.05
PWV (m/s)	Control (n = 15)	10.5 ± 0.42	10.1 ± 0.41	-3.63% ± 1.47%	> 0.05
	ω-3 PUFAs (n = 21)	11.3 ± 0.48	9.0 ± 0.44	-18.9% ± 3.9%	< 0.01

Results in the table are presented as % change from baseline (Δ%, Mean ± SEM) and absolute values; DCAN: diabetic cardiac autonomic neuropathy; T2D: type 2 diabetes; AIxao: aorta augmentation index; PWV: pulse wave velocity; AIxbr: brachial augmentation index; SEM: standard error of the mean.

Administration of ω-3 PUFAs to patients with confirmed DCAN and T2D was followed by the decrease of the PWV by -11.6 % ± 2.09 % (p < 0.05) and AIxao by -16.2 % ± 3.12 % (p < 0.01) during the active period; PWV by -18.9% ± 3.9% (p < 0.01), AIxao by -11.2% ± 4.2% (p < 0.05) and AIxbr by -98.0% ± 18.1% (p < 0.05) - passive period of day (compared to the control group).

Discussions

The antioxidative, hypotensive and anti-inflammatory properties of ω-3 PUFAs, as well as their ability to improve endothelial cell function can serve as explanation of arterial stiffness parameters improvement after their

administration. The systematic review by Pase et al. (2011) [11] summarized the peculiarities of ω-3 PUFAs influence on arterial stiffness parameters. Ten studies met the inclusion criteria with 550 patients randomized to take placebo or ω-3 PUFAs (total daily dose from 0.64 to 3.0 g) for a treatment duration from 6 to 105 wks. Patients with DM, dyslipidemia, hypertension, overweight and healthy subjects were included to this studies. The prescription of ω-3 PUFAs was associated with improvement of arterial stiffness parameters and this effect was not connected to changes in body mass index, heart rate and blood pressure (BP). At a recent time in a larger randomized controlled trial on healthy persons the same author showed that a high dose ω-3 fish oil consumption (6 g/day) could reduce two indirect measurements of arterial stiffness and central BP, namely aortic pulse pressure and AIxao [11,7].

The inverse association between the level of circulatory ω-3 PUFAs or of its consumption and the brachial artery cross-sectional diameter has been reported by some authors. It was demonstrated that the content of ω-3 PUFAs in membrane is directly associated with the degree of vasodilatation observed after sublingual nitrate intake, that can serve as evidence of their beneficial effect on the vascular wall [7]. Ω-3 PUFA dose-dependently prevent the diabetes manifestation, decrease insulin resistance (IR), improve the sensitivity of platelets to collagen and ADP, lead to positive changes in endothelial cells migration and the coagulation parameters, enhance and inhibit smooth muscle cells proliferation [5,18].

Others investigators have posited that administration of ω-3 PUFAs can reduce the risk of cardiovascular diseases through anti-thrombogenic, anti-inflammatory, anti-arrhythmic, hypotensive, hypotriacyl-glycerolaemic mechanisms, ability to stimulate endothelial nitric oxide and inhibit atherosclerotic plaque growth. There is some evidence to indicate that cardioprotective effects of ω-3 PUFAs are associated with the improvement in arterial stiffness [11,13,19].

Omega-3 PUFAs inhibit the synthesis of cholesterol in the liver, its intestinal absorption, in terms of experimental diabetes prevent the development of IR, increase levels of glucose transporters GLUT4, have a positive effect on the indirect age slowing of blood flow in the brain, improve utilization of glucose in hypertensive rats under stress, there is no influence on the hypertension and overweight development [14,5].

Effective influence of ω-3 PUFAs is probably connected to their effects on glucose metabolism and IR (IR reduces in the muscle > fat >> liver); lipid metabolism; slightly reduces BP, improves antioxidant protection and endothelial function, reduces proinflammatory state [5,15,18].

We reported that prescription of ω-3 PUFAs is associated with improvement of a vegetative condition (questionnaire Wayne): sum of score was decreased significantly, positive changes of temporal and spectral parameters of heart rate variability, corrected QT interval was observed; increasing of the period of inactivity platelet aggregation, inhibition of the first phase aggregation, decreasing of their hyperactive state, the tendency to normalization of the status of prostacyclin I_2-thromboxane A_2 system was determined [5].

The combination of the positive effects of ω-3 PUFAs on arterial stiffness parameters, NT-proBNP concentration, certain lipids in the blood, and also noted earlier moderate hypotensive effects of ω-3 PUFAs [20,21] demonstrates the feasibility of their prescription to patients with diabetic DCAN [5,20].

Conclusions

In subjects with T2D and DCAN treatment with ω-3 PUFAs resulted in a significant decrease of AIxao, PWV during the active period of the day and decrease of AIxao, AIxbr and PWV during the passive period of the day compared with the data from a comparation group. Therefore, the prescription of ω-3 PUFAs improved arterial stiffness indices in patients with confirmed DCAN and T2D. The effectiveness of ω-3 PUFAs is not connected with optimization of glycemic control, but is rather the result of a direct drug action on the studied parameters.

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