WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 8, Issue 11, 38-50. Research Article ISSN 2277– 7105

OMEGA-3 POLYUNSATURATED FATTY ACIDS, LIPID PROFILE, INSULIN RESISTANCE AND DIABETIC CARDIAC AUTONOMIC NEUROPATHY

Samir Ajmi[1], Victoria A. Serhiyenko[1]*, Ludmila M. Serhiyenko[2], Alexander A. Serhiyenko[1]

[1]Department of Endocrinology, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine.

[2]Department of Medical Biology, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine.

Article Received on
01 August 2019,
Revised on 21 August 2019,
Accepted on 11 Sept. 2019,

DOI: 10.20959/wjpr201911-15867

***Corresponding Author**
Victoria A. Serhiyenko
Department of Endocrinology, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine.

ABSTRACT

Background: The significance of cardiac autonomic neuropathy (CAN) in patients with type 2 diabetes mellitus (T2DM) has been not fully appreciated and there is no unified treatment algorithm. **Aim:** The aim of study was to investigate the effects of ω-3 polyunsaturated fatty acids (ω-3 PUFAs) on blood lipid profile and insulin resistance (IR) parameters in patients with T2DM and definite CAN. **Patients and Methods:** The study involved 33 patients with T2DM and definite CAN. Patients were allocated into two treatment groups: 1st group - 15 patients received standard hypoglycaemic therapy - control (n = 15); 2nd group (n = 18) - standard hypoglycaemic therapy and 1 capsule/day of the ω-3 PUFAs (1 g, including ~90 % ω-3 PUFAs) for three months. The concentrations of glucose, glycated haemoglobin A1c, immunoreactive insulin in the blood were determined. Lipid metabolism was assessed by the concentration of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) measurements. The insulin resistance Homeostasis model assessment, atherogenic coefficient (AC), TG/LDL-C, TG/TC, TG/LDL-C and TG glucose (TyG) index were calculated. **Results:** Obtained results of our study could witness that the prescription of ω-3 PUFAs was accompanied by a statistically significant decrease in TG concentration; AC, TG/LDL-C, TG/TC, TG/LDL-C, TyG index parameters and increase

in HDL-C levels (compared to control). **Conclusions:** Obtained results justify the appropriateness of ω-3 PUFAs prescriptions to patients with T2DM and definite CAN.

KEYWORDS: Type 2 diabetes mellitus, Cardiac autonomic neuropathy, Lipids, Insulin resistance, Ω-3 polyunsaturated fatty acids.

INTRODUCTION

It was estimated that there were 415 million people with diabetes mellitus (DM) aged 20-79 years in 2015, and the number was predicted to rise to 642 million by 2040.[1] The development of cardiac autonomic neuropathy (CAN) is associated with the lesion of the autonomic nervous system, and maybe accompanied by coronary vessels ischemia, arrhythmias, "silent" myocardial infarction, severe orthostatic hypotension and sudden death syndrome.[2-6] Therefore, the problem of effective treatment of CAN is particularly relevant. Pathogenetic treatment of CAN includes: balanced diet and physical activity; reducing insulin resistance; optimization of glycaemic control; treatment of dyslipoproteinemia (DLP); correction of metabolic abnormalities in myocardium; prevention and treatment of thrombosis; use of aldose reductase inhibitors; γ-linolenic acid, acetyl-L-carnitine, antioxidants, use of ω-3 polyunsaturated fatty acids (ω-3 PUFAs), vasodilators, fat-soluble vitamin B_1, aminoguanidine; symptomatic treatment of concomitant diseases and syndromes [hypertension, coronary heart disease (CHD), heart failure and arrhythmias] and others.[7-10] Numerous studies report salutary effects of ω-PUFAs, i.e. eicosapentaenoic (EPA) and docosahexaenoic acid (DHA) on cardiovascular diseases (CVD) risk factors. These effects include lowering of serum triglyceride (TG) by reducing of hepatic TG production; lowering of blood pressure (BP) by improving of endothelial cell function; decreasing of platelet aggregation by reducing of prothrombotic prostanoids; decreasing inflammation *via* reduction in 4-series leukotrienes production; protection from arrhythmias by modulation of electrophysiological properties of cardiomyocytes. Systematic meta analysis suggests that high doses of ω-3 PUFAs (~3 g/day) produce a small, but significant decrease in systolic BP in older and hypertensive subjects.[11-12]

The aim of this study was to investigate the effects of omega-3 polyunsaturated fatty acids on blood lipid profile, triglyceride-glucose index and insulin resistance parameters in patients with type 2 diabetes mellitus and definite cardiac autonomic neuropathy.

MATERIALS AND METHODS

The study involved 33 patients with type 2 DM (T2DM) and definite CAN. Median age of patients was 55.1 ± 0.63 yrs, disease duration - 3.52 ± 0.29 yrs and median glycated haemoglobin (HbA1c) - 7.09% ± 0.12%. CAN was diagnosed according to previously proposed criteria.[2] The work was done according to the principles of the Helsinki Declaration II and was approved by the Medical Ethics Committee of Danylo Halytsky Lviv National Medical University. All participants signed informed consent prior to their inclusion into the study. First group received traditional antihyperglycaemic therapy (n = 15, control group) for three months; patients in group 2 (n = 18), received in addition to standard treatment 1 capsule/day of the ω-3 PUFAs for three months. The capsule contains 1 g, including ~90 % ω-3 PUFAs, mainly EPA and DHA and 4 mg of α-tocopherol acetate. The duration of the treatment was three months. Clinical characteristics of studied patients with T2DM and definite CAN are given in Table 1.

Table 1: Baseline characteristics of patients included in this study.

Parameter	Patients with T2DM and definite CAN (n = 33)	
	Control (n = 15)	Ω-3 PUFAs (n = 18)
	Group 1	Group 2
Age (years)	55.33 ± 0.95	54.83 ± 0.87
Gender		
Male (%)	8/53.3%	10/55.6%
Female (%)	7/46.7%	8/44.4%
Diabetes duration (years)	3.6 ± 0.42	3.44 ± 0.43
BMI (kg/m^2)	28.89 ± 0.16	28.18 ± 0.33
Medications		
ACE inhibitors (%)	12/80%	14/77.8%
β-blockers (%)	3/20%	4/22.2%
Metformin (%)	11/73.3%	12/66.7%
Sulfonylurea (%)	1/6.7%	1/5.5%
Combined hypoglycaemic therapy (%)	3/20%	5/27.8%
Hypertension (%)	12/80%	16/88.9%

T2DM: type 2 diabetes mellitus; CAN: cardiac autonomic neuropathy; BMI: body mass index; ACE: angiotensin-converting enzyme.

The concentration of glucose in the blood was determined by the glucose oxidase method while HbA1c level was assessed by using a highly sensitive method of ion-exchange liquid chromatography with D-10 analyzer and BIO-RAD reagents (United States). Determination of immunoreactive insulin (IRI) was performed using commercial kits from Immunotech

insulin immunoradiometric assay reagents (Czech Republic). Lipid metabolism was assessed by the concentration of total cholesterol (TC), TG, low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C); atherogenic coefficient (AC), TG/LDL-C, TG/TC, TG/LDL-C, TG/HDL-C parameters. The TG glucose (TyG) index was calculated by the Ln [fasting TG (mg/dL) x fasting glucose (mg/dL)/2].[13] TyG index, the product of fasting glucose and TG in the blood, has been proposed as a simple method for determining insulin resistance (IR) in healthy subjects.[14-15] The use of the homeostasis model assessment (HOMA) IR (HOMA-IR),[16,17] the insulin suppression test,[14] and the hyperinsulinemic-euglycemic clamp.[16,17] suggested that the TyG index correlates with IR.[18] TyG indexes are reported to be elevated in T2DM patients compared to parameters in patients with prediabetes.[18-20] The lipid fractions were determined by using HUMAN reagents (Germany) for the analyzer Humanlayzer 2000. HOMA-IR index was calculated according to the formula: fasting IRI (mcIU/mL) x fasting glucose (mmol/L)/22.5.[21] Resting 12-lead surface electrocardiography (ECG) with a paper speed of 25 mm/s and a signal size of 10 mm/mV was recorded in the morning period. We performed resting ECG analysis included measurement of the following parameters: heart rhythm, heart rate, conduction intervals, and Holter-ECG [(ECG "EC-3H" ("Labtech," Hungary)] analysis included measurement of 24 hours ECG, circadian indexes and heart rate variability parameters.

Statistical analysis

Statistical analysis was based on the variational method using a statistical parametric t-test, nonparametric Wilcoxon t-test, and Fisher's Pearson correlation coefficient. Data are presented as mean ± standard error of the mean (SEM). All tests were performed using the ANOVA (MicroCal Origin v. 8.0) software. Statistical significance was set at $p < 0.05$.

RESULTS

We found out that the HbA1c of patients with T2DM and definite CAN was not statistically significantly influenced by the treatment ($p > 0.05$). Changes of HbA1c, IRI and HOMA-IR parameters among patients with T2DM and definite CAN after 3-mo of ω-PUFAs therapy are given in Table 2.

Table 2: Changes in the values of some metabolism indicators in patients with T2DM with definite CAN after 3-months of ω-3 PUFAs treatment (Δ%, Mean ± SEM).

Parameter	Patients with T2DM and definite CAN (n = 33)				
	Groups	Baseline	After treatment	% change from baseline	p
HbA1c, %	Control (n = 15)	7.17±0.18	7.21±0.19	+0.6±1.07	> 0.05
	Ω-3 PUFAs (n = 18)	7.03±0.17	7.07±0.14	+0.87±1.22	> 0.05
IRI, мcIU/L	Control (n = 15)	27.39±2.13	26.01±2.25	-6.43±3	> 0.05
	Ω-3 PUFAs (n = 18)	25.07±2.65	23.44±2.34	-4.23±5.62	> 0.05
HOMA-IR	Control (n = 15)	9.04±0.99	8.46±0.99	-6.12±4.06	> 0.05

The results are presented as absolute values and as % change from baseline (Δ%, Mean ± SEM); T2DM: type 2 diabetes mellitus; CAN: cardiac autonomic neuropathy; ω-3 PUFAs: ω-3 polyunsaturated fatty acids; HbA1c: glycated hemoglobin A1c IRI: immunoreactive insulin; IR; insulin resistance; HOMA-IR: homeostasis model assessment IR.

As a result of our study, we found out that the use of ω-3 PUFAs do not affect the concentration of IRI and HOMA-IR parameters. As we have previously reported, the definite CAN in patients with T2DM is characterized by an increase in IRI concentration (+136.04%) compared to healthy volunteers ($p < 0.001$); compared to patients without CAN ($p < 0.001$); compared to patients with sublinical CAN ($p < 0.001$), and HOMA-IR (+240.82% compared to healthy volunteers ($p < 0.001$); compared to patients without CAN ($p < 0.01$). Therefore, the most statistically significant hyperinsulinaemia (determined according to the IRI concentration) as well as IR (HOMA-IR) were verified in patients with T2DM and definite CAN[5]. The definite CAN is characterized by a significant increase in the content of TC, TG; LDL-C, and a significant decrease in the concentration of HDL-C[5]. Changes of lipid parameters among patients with T2DM and definite CAN after 3-mo of ω-PUFAs therapy are given in Table 3.

Table 3: Changes in the values of some lipid parameters in patients with T2DM with definite CAN after 3-months of ω-3 PUFAs treatment (Δ%, Mean ± SEM).

Parameter	Patients with T2DM and definite CAN (n = 33)				
	Groups	Baseline	After treatment	% change from baseline	p
TC	Control (n = 15)	6.59 ± 0.18	6.13 ± 0.15	-6.73 ± 1.09	> 0.05
	Ω-3 PUFAs (n = 18)	6.0 ± 0.2	5.64 ± 0.24	-5.52 ± 3.16	> 0.05
LDL-C	Control (n = 15)	4.59 ± 0.16	4.25 ± 0.17	-8.27 ± 1.44	> 0.05
	Ω-3 PUFAs (n = 18)	4.09 ± 0.18	3.78 ± 0.27	-8.08 ± 5.58	> 0.05

HDL-C	Control (n = 15)	0.84 ± 0.03	0.87 ± 0.03	+4.09 ± 0.97	> 0.05
	Ω-3 PUFAs (n = 18)	0.78 ± 0.03	0.9 ± 0.05	+9.73 ± 2.57	**< 0.05**
TG	Control (n = 15)	2.52 ± 0.12	2.31 ± 0.11	-8.28 ± 1.17	> 0.05
	Ω-3 PUFAs (n = 18)	2.47 ± 0.15	1.62 ± 0.09	-33.35 ± 2.73	**< 0.001**

The results are presented as absolute values and as % change from baseline (Δ%, Mean ± SEM); T2DM: type 2 diabetes mellitus; CAN: cardiac autonomic neuropathy; ω-3 PUFAs: ω-3 polyunsaturated fatty acids; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride.

Treatment with the ω-3 PUFAs among patients with T2DM and definite CAN lead to a significant increase of the HDL-C level [+9.73 ± 2.57% ($p < 0.05$)] and decrease TG concentration [-33.35 ± 2.73%, $p < 0.001$). Obtained results of this study could prove that prescription of ω-3 PUFAs is accompanied by hypolipidaemic effect without influence on glucose metabolism. Changes in the values of some lipid ratios in patients with T2DM with definite CAN after 3-months of treatment with ω-3 PUFAs are presented in the Table 4.

Table 4: Changes in the values of some lipid ratios in patients with T2DM with definite CAN after 3-months of ω-3 PUFAs treatment (Δ%, Mean ± SEM).

Parameter	**Patients with T2DM and definite CAN (n = 33)**				
	Groups	**Baseline**	**After treatment**	**% change from baseline**	**p**
AC	Control (n = 15)	7.05 ± 0.43	6.2 ± 0.37	-11.79 ± 1.38	> 0.05
	Ω-3 PUFAs (n = 18)	6.9 ± 0.47	5.6 ± 0.44	-20.17 ± 7.24	**< 0.05**
TG/LDL-C	Control (n = 15)	0.55 ± 0.02	0.54 ± 0.03	-0.39 ± 2.06	> 0.05
	Ω-3 PUFAs (n = 18)	0.61 ± 0.03	0.46 ± 0.03	-22.2 ± 5.61	**< 0.001**
TG/TC	Control (n = 15)	0.38 ± 0.01	0.37 ± 0.02	-1.07 ± 1.8	> 0.05
	Ω-3 PUFAs (n = 18)	0.41 ± 0.016	0.29 ± 0.01	-28.34 ± 3.47	**< 0.001**
TG/HDL-C	Control (n = 15)	3.09 ± 0.21	2.74 ± 0.2	-11.65 ± 1.58	> 0.05
	Ω-3 PUFAs (n = 18)	3.29 ± 0.27	1.89 ± 0.15	-41.22 ± 2.24	**< 0.001**
TC/LDH-C /HDL-C	Control (n = 15)	1.75 ± 0.06	1.7 ± 0.07	-2.74 ± 1.74	> 0.05
	Ω-3 PUFAs (n = 18)	1.91 ± 0.05	1.77 ± 0.06	-6.87 ± 3.08	> 0.05
TyG index	Control (n = 15)	9.53 ± 0.06	9.44 ± 0.05	-0.89 ± 0.39	> 0.05
	Ω-3 PUFAs (n = 18)	9.46 ± 0.08	9.05 ± 0.08	-4.24 ± 0.68	**< 0.001**

The results are presented as absolute values and as % change from baseline, (Δ%, Mean ± SEM); T2DM: type 2 diabetes mellitus; CAN: cardiac autonomic neuropathy; ω-3 PUFAs: ω-3 polyunsaturated fatty acids; AC: atherogenic coefficient; TG/LDL-C: triglyceride/low-density lipoprotein cholesterol ratio; TG/TC: triglyceride/total cholesterol ratio; TG/LDL-C:

triglyceride/low-density lipoprotein cholesterol ratio; TG/HDL-C: triglyceride/high-density lipoprotein cholesterol ratio; TyG: TG glucose index.

As a result of our study, we found out that the use of ω-3 PUFAs was accompanied by a statistically significant decrease in the AC, TG/LDL-C, TG/TC, TG/HDL-C, and TyG index parameters (compared with the control group) (Table 4).

DISCUSSION

Several experimental studies have shown that long-chain ω-PUFAs 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 IR in experimental diabetes, increase the level of glucose transporter 4 in skeletal muscles, have a positive effect on age related decrease of blood flow in the brain and improve glucose utilization under stress; there isn't any influence on the development of hypertension and metabolic syndrome. Ω-3 PUFAs decrease level of BP, dose-dependent prevent the development of T2DM, IR, contribute to positive changes of blood coagulation parameters; enhance endothelial cell migration and inhibits the proliferation of smooth muscle cells.[22] A meta-analysis of 18 studies found a significant effect of fish oil to lower TG concentrations and increase HDL-C in the blood; while there were no statistically significant changes in preprandial glucose, HbA1c, TC, LDH-C levels. Ω-3 PUFAs may affect the IR and glucose homeostasis by inhibition of IR in the muscle tissue > adipose tissue >> liver, inhibition of insulin secretion, which defer the development of T2DM; and on the state of lipid metabolism (in particular, reduce the concentration of TG, very low density-lipoprotein cholesterol (VLDL-C), increase of HDL-C, improve lipid profile by mixed hyperlipidaemia, slightly decrease BP, improve endothelial function, have an positive impact on the antioxidant status and inflammatory reactions[23]. Ω-3 PUFAs decrease VLDL assembly and secretion, resulting in diminished TG production, through a decreased sterol receptor element binding protein-1c activity.[24,23]

Clinical trials clearly suggest beneficial effects of ω-3 PUFAs consumption on plasma TG levels. A review of placebo-controlled human studies concludes that an average intake of 3–4 $g \cdot day^{-1}$ of ω-3 PUFAs decreases serum TG concentrations by 25–30% in a dose-dependent manner. The same intake does not affect TC but increases LDL levels by 5-10% and HDL by 1-3%.[23] The increase in LDL is mainly through a rise in amounts of the larger, more buoyant and potentially less atherogenic LDL particles, whereas the smaller, denser and potentially

more atherogenic LDL particles decrease.[22,23,25] Some studies reported that prescription of EPA and DHA to patients with severe lipid metabolism disorders (in particular with hypertriglyceridemia, primary hypercholesterolaemia, combined DLP, family combined DLP, CHD, and persistent hypertriglyceridemia) decreased TC levels or did not affect it and increased LDL-C, HDL-2 and apolipoprotein A concentrations.[26] Results of several studies, including GISSI and JELIS, showed only insignificant changes of TG levels.[22,23]

Prescription of ω-3 PUFAs resulted in positive changes in lipid metabolism profile in a patient with T2DM and DLP, which was characterized by increased TG and reduced HDL-C levels. However, studies of ω-3 PUFAs prescription to patients with DM without diagnosed CHD (despite accumulated evidence that T2DM showing as the equivalent of CHD[27-29] are few and obtained results do not suggest their effectiveness. The highly concentrated pharmaceutical preparation Omacor™ (Pronova Biocare, Lysaker, Norway), known as Lovaza™ (GlaxoSmithKline, St Petersberg, FL, US) in North America is approved by the FDA as an adjunct to diet to reduce very high TG levels (≥ 500 $mg \cdot dL^{-1}$) in adults. Each 1-g capsule of ω-3-acid ethyl esters contains ethyl esters of EPA (0.465 g) and DHA (0.375 g). Patients take a q.d. dose of 4-g or two 2-g doses (two capsules b.i.d.).[30] Clinical trials have shown that administration of 4 $g \cdot day^{-1}$ of Lovaza™ results in a decrease in TG levels of 30–50%; does not affect the efficacy of statins.[31] In patients with combined DLP, co-administration of Lovaza™ with statins was a safe and effective means of lowering serum TG, despite the persistent high TG levels when the patients received statins alone.[32] The relative risk of CHD in patients who consumed fish less than one time per month was 0.70, 1-3 times a month - 0.60, once a week - 0.64, 5 times a week – 0.36. Thus, a higher consumption of fish (including ω-3 PUFAs) contributed to the reduction of CHD incidence and reduced total mortality rate significantly. However, effects of ω-3 PUFAs on the development/progression of CHD and mortality in patients with DM are not entirely understood. The question of the feasibility and additional benefits of ω-3 PUFAs administration in combination with statins to avoid polypragmasia in the treatment of diabetic vascular disorders is open.[26,23]

Therefore, dietary consumption of ω-3 PUFAs is recommended in international guidelines for the general population to prevent the occurrence of CHD. However, the precise mechanisms underlying the cardioprotective effects of ω-3 PUFAs are not fully understood. Ω-3 PUFAs can be incorporated into the phospholipid bilayer of cell membranes and can affect

membrane fluidity, lipid microdomain formation, and signaling across membranes. Ω-3 PUFAs also modulate the function of membrane ion channels, such as Na^+ and L-type Ca^{2+} channels, to prevent lethal arrhythmias. Moreover, ω-3 PUFAs also prevent the conversion of arachidonic acid into pro-inflammatory eicosanoids by serving as an alternative substrate for cyclooxygenase or lipoxygenase pathways, resulting in the production of less potent products. In addition, a number of enzymatically oxygenated metabolites derived from ω-3 PUFAs were recently identified as anti-inflammatory mediators. These ω-3 metabolites may contribute to the beneficial effects against CHD that are attributed to ω-3 PUFAs.[33,34]

CONCLUSION

Development of hyperinsulinemia and IR among patients with T2DM and CAN are accompanied by atherogenic changes in lipid profile namely by an increase in TC, TG, LDL-C, AC, TyG index and decrease in HDL-C. The most pronounced atherogenic changes observed among patients with definite CAN. Obtained results could wittness about the essential importance of hyperinsulinaemia, IR and DLP in the pathogenesis of the CAN. Prescription of ω-3PUFAs contributed to a statistically significant decrease in the concentration of TC, LDL-C, TG, AC, TG/LDL-C, TG/TC, TG/HDL-C, TyG index parameters, and an increase in the content of HDL-C (compared to the control). Our results suggest that the efficacy of ω-3 PUFAs is not associated with improved glycemic control of T2DM in patients with definite stage of CAN, but is rather the result of a direct effect of the pharmacological agent on the investigated metabolic indexes. Therefore, the appointment of ω-3PUFAs is necessary in the treatment of DLP in patients with T2DM with definite CAN. However, existing data are not consistent perhaps due to a significant heterogeneity (variable doses of ω-3 PUFAs, different duration of intake, different populations, and end-points) in the interventional studies. For prevention/treatment of CAN events supplementation with ω-3 PUFAs should be integrated into a more global strategy that includes focusing on other components of a healthy lifestyle (diet, weight control, physical activity, smoking cessation) and on tight control of glucose and lipid profile when indicated. Thus, further research to understand the mechanism of action and confirm the beneficial effect of ω-3 PUFAs on BP profile, artery stiffness, and heart rate variability parameters is needed.

ACKNOWLEDGMENTS

Conflict of interests: There are no ethical/legal conflicts involved in the article. There are no conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject of their manuscript.

Authorship: All the listed authors contributed significantly to conception and design of study, acquisition, analysis and interpretation of data and drafting of manuscript, to justify authorship.

FUNDING

No any grant or funds have been received for this study.

REFERENCES

1. Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract., 2017; 128(2): 40-50. doi: 10.1016/j.diapres.2017.03.024.
2. Spallone V, Ziegler D, Freeman R, Bernardi L, Frontoni S, Pop-Busui R, et al. Toronto Consensus Panel on Diabetic Neuropathy. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. Diabetes Metab Res Rev., 2011; 27(7): 639-653. doi: 10.1002/dmrr.1239.
3. Standards of Medical Care in Diabetes-2017: Summary of Revisions. Diabetes Care, 2017; 40(Suppl 1): S4-S5. doi: 10.2337/dc17-S013.
4. Serhiyenko VA, Serhiyenko AA. Diabetic cardiac autonomic neuropathy: Do we have any treatment perspectives? World J Diabetes, 2015; 6(2): 245-258. doi: 10.4239/wjd.v6.i2.245.
5. Serhiyenko V, Serhiyenko A. Diabetic cardiovascular neuropathy. Stavropol; Logos Publishers, 2018. doi: 10.18411/dia012018.49.
6. Serhiyenko VA, Serhiyenko AA. Diabetic cardiac autonomic neuropathy. In: Saldaña JR (eds.), Diabetes Textbook: Clinical principles, patient management and public health issues. Basel; Springer Nature Switzerland AG, 2019; 825-850. doi: 10.1007/978-3-030-11815-0.
7. Vinik AI, Erbas T, Casellini CM. Diabetic cardiac autonomic neuropathy, inflammation and cardiovascular disease. J Diabetes Investig., 2013; 4(1): 4-18. doi: 10.1111/jdi.12042.

8. Balcıoğlu AS, Müderrisoğlu H. Diabetes and cardiac autonomic neuropathy: clinical manifestations, cardiovascular consequences, diagnosis and treatment. World J Diabetes, 2015; 6(1): 80-91. doi: 10.4239/wjd.v6.i1.80.
9. Tandon N, Ali MK, Narayan KM. Pharmacologic prevention of microvascular and macrovascular complications in diabetes mellitus: implications of the results of recent clinical trials in type 2 diabetes. Am J Cardiovasc Drugs, 2012; 12(1): 7-22. doi: 10.2165/11594650-000000000-00000.
10. Serhiyenko VA, Serhiyenko LM, Serhiyenko AA. Omega-3 polyunsaturated fatty acids in the treatment of diabetic cardiovascular autonomic neuropathy: A review. In: Moore SJ, ed. Omega-3: Dietary sources, biochemistry and impact on human health. New York: Nova Science Publishers, 2017: 79-154. ISBN: 978-1-53611-824-7. print. ISBN: 978-1-53611-839-1. e-book.
11. Bonafini S, Antoniazzi F, Maffeis C, Minuz P, Fava C. Beneficial effects of omega-3 PUFA in children on cardiovascular risk factors during childhood and adolescence. Prostaglandins Other Lipid Mediat., 2015; 120(7): 72-79. doi: 10.1016/j.prostaglandins.2015.03.006.
12. Jeppesen C, Schiller K, Schulze MB. Omega-3 and omega-6 fatty acids and type 2 diabetes. Curr Diab Rep., 2013; 13(2): 279-288. doi: 10.1007/s11892-012-0362-8.
13. Simental-Mendia LE, Rodriguez-Moran M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. Metab Syndr Relat Disord., 2008; 6(4): 299-304. doi: 10.1089/met.2008.0034.
14. Abbasi F, Reaven GM. Comparison of two methods using plasma triglyceride concentration as a surrogate estimate of insulin action in nondiabetic subjects: triglycerides x glucose versus triglyceride/high-density lipoprotein cholesterol. Metabolism, 2011; 60(12): 1673-1676. doi: 10.1016/j.metabol.2011.04.006.
15. Du T, Yuan G, Zhang M, Zhou X, Sun X, Yu X. Clinical usefulness of lipid ratios, visceral adiposity indicators, and the triglycerides and glucose index as risk markers of insulin resistance. Cardiovasc Diabetol., 2014; 13: 146. doi: 10.1186/s12933-014-0146-3.
16. Guerrero-Romero F, Simental-Mendia LE, Gonzalez-Ortiz M, Martinez-Abundis E, Ramos-Zavala MG, Hernandez-Gonzalez SO, et al. The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic-hyperinsulinemic clamp. J. Clin. Endocrinol. Metab., 2010; 95(7): 3347-3351. doi: 10.1210/jc.2010-0288.

17. Vasques AC, Novaes FS, de Oliveira Mda S, Souza JR, Yamanaka A, Pareja JC, et al. TyG index performs better than HOMA in a Brazilian population: a hyperglycemic clamp validated study. Diabetes Res Clin Pract., 2011; 93(3): e98-e100. doi: 10.1016/j.diabres.2011.05.030.
18. Kim HJ, Moon JS, Park IR, Kim JH, Yoon JS, Won KC, et al. A novel Index using soluble CD36 is associated with the prevalence of type 2 diabetes mellitus: comparison study with triglyceride-glucose index. Endocrinol Metab., 2017; 32(3): 375-382. doi: 10.3803/EnM.2017.32.3.375.
19. Lee SH, Kwon HS, Park YM, Ha HS, Jeong SH, Yang HK, et al. Predicting the development of diabetes using the product of triglycerides and glucose: the Chungju Metabolic Disease Cohort (CMC) study. PLoS One, 2015; 9(2): e90430. doi: 10.1371/journal.pone.0090430.
20. Navarro-Gonzalez D, Sanchez-Inigo L, Pastrana-Delgado J, Fernandez-Montero A, Martinez JA. Triglyceride-glucose index (TyG index) in comparison with fasting plasma glucose improved diabetes prediction in patients with normal fasting glucose: the Vascular-Metabolic CUN cohort. Prev Med., 2016; 86: 99-105. doi: 10.1016/j.ypmed.2016.01.022.
21. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia, 1985; 28(7): 412-419. doi: 10.1007/bf00280883.
22. von Schacky C, Harris WS. Cardiovascular benefits of omega-3 fatty acids. Cardiovasc Res., 2007; 73(2): 310-315. doi: 10.1016/j.cardiores. 2006.08.019.
23. de Roos B, Mavrommatis Y, Brouwer IA. Long-chain n-3 polyunsaturated fatty acids: new insights into mechanisms relating to inflammation and coronary heart disease. Br J Pharmacol., 2009; 158(2): 413-428. doi: 10.1111/j.1476-5381.2009.00189.x.
24. Jump DB. N-3 polyunsaturated fatty acid regulation of hepatic gene transcription. Curr Opin Lipidol., 2008; 19(3): 242-247. doi: 10.1097/MOL.0b013e3282ffaf6a.
25. Lee MW, Park JK, Hong JW, Kim KJ, Shin DY, Ahn CW, et al. Beneficial effects of omega-3 fatty acids on low density lipoprotein particle size in patients with type 2 diabetes already under statin therapy. Diabetes Metab J., 2013; 37(3): 207-211. doi: 10.4093/dmj.2013.37.3.207.

26. Kandasamy N, Joseph F, Goenka N. The role of omega-3 fatty acids in cardiovascular disease, hypertriglyceridemia and diabetes mellitus. Br J Diabet Vasc Dis., 2008; 8(3): 121-128. doi: 10.1177/147465140800 80030301.
27. Colussi G, Catena C, Sechi LA. ω-3 polyunsaturated fatty acids effects on the cardiometabolic syndrome and their role in cardiovascular disease prevention: an update from the recent literature. Recent Pat Cardiovasc Drug Discov., 2014; 9(2): 78-96. PMID: 26206120.
28. Serhiyenko V, Serhiyenko L, Serhiyenko A. Omega-3 polyunsaturated fatty acids, metabolic syndrome and diabetes mellitus. Curre Res Diabetes Obes J., 2018; 5(4): 555670. doi: 10.19080/CRDOJ.2018.05.555670.
29. Serhiyenko VA, Serhiyenko AA. Cardiac autonomic neuropathy: Risk factors, diagnosis and treatment. World J Diabetes, 2018; 9(1): 1-24. doi: 10.4239/wjd.v9.i1.1.
30. Bradberry JC, Daniel E, Hilleman DE. Overview of omega-3 fatty acid therapies. P T., 2013; 38(11): 681-691. PMID: 24391388 PMCID: PMC3875260.
31. McKenney JM, Swearingen D, Di Spirito M, Doyle R, Pantaleon C, Kling D, et al. Study of the pharmacokinetic interaction between simvastatin and prescription omega-3-acid ethyl esters. J Clin Pharmacol., 2006; 46(7): 785-791. doi: 10.1177/0091270006289849.
32. Davidson MH, Stein EA, Bays HE, Maki KC, Doyle RT, Shalwitz RA, et al. COMBination of prescription omega with simvastatin (COMBOS) investigators. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. Clin Ther., 2007; 29(7): 1354-1367. doi: 10.1016/j.clinthera.2007.07.018.
33. Calder PC. Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms and clinical relevance. Biochim Biophis Acta, 2015; 1851: 469-484. doi: 10.1016/j.bbalip.2014.08.010.
34. Endo J, Arita M. Cardioprotective mechanism of omega-3 polyunsaturated fatty acids. J Cardiol., 2016; 67: 22-27. doi: 10.1016/*j*.jjcc.2015.08.002.