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**Diabetic cardiac autonomic neuropathy: Do we have any treatment perspectives?**

Serhiyenko VA *et al*. Treatment of diabetic cardiac autonomic neuropathy

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**Abstract**

Cardiac autonomic neuropathy (CAN) is a serious and common complication of diabetes mellitus (DM). Despite its relationship to an increased risk of cardiovascular mortality and its association with multiple symptoms and impairments, the significance of CAN has not been fully appreciated. CAN among DM patients is characterized by lesion of nerve fibers in the sympathetic and parasympathetic nervous system, is diagnosed unsatisfactorily and is one of the leading causes of heart arrhythmias, “silent” myocardial infarction, sudden death syndrome. The aim of this article is to review the latest evidence and own data regarding the treatment and the treatment perspectives for diabetic CAN. Lifestyle modification, intensive glycemic control might prevent development or progression of CAN. Pathogenetic treatment of CAN includes: balanced diet and physical activity; optimization of glycemic control; treatment of dyslipoproteinemia; correction of metabolic abnormalities in myocardium; prevention and treatment of thrombosis; use of aldose reductase inhibitors; dihomo-γ-linolenic acid (DGLA), acetyl-L-carnitine, antioxidants, first of all α-lipoic acid (α-LA), use of long-chain ω-3 and ω-6 polyunsaturated fatty acids (ω-3 and ω-6 PUFAs), vasodilators, fat-soluble vitamin B1, aminoguanidine; substitutive therapy of growth factors, in severe cases-treatment of orthostatic hypotension. The promising methods include research and use of tools that increase blood flow through the vasa vasorum, including prostacyclin analogues, thromboxane A2 blockers and drugs that contribute into strengthening and/or normalization of Na+, K+-ATPase (phosphodiesterase inhibitor), α-LA, DGLA, ω-3 PUFAs, and the simultaneous prescription of α-LA, ω-3 PUFA and DGLA.

**Key words:** Diabetes mellitus; Cardiac autonomic neuropathy; Postural hypotension; treatment

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**Core tip:** Cardiac autonomic neuropathy (CAN) is a serious complication of diabetes mellitus, that is strongly associated with increased risk of cardiovascular mortality. CAN manifests in a spectrum of things, ranging from resting tachycardia and fixed heard rate to development of “silent” myocardial infarction. Although it is common complication, the significance of CAN has not been fully appreciated and there are no unified treatment algorithms for today. In this review we have analyzed the effectiveness of lifestyle modification, prescription of α-lipoic acid, aldose reductase inhibitors; γ-linoleic acid, acetyl-L-carnitine, antioxidants, long-chain ω-3 polyunsaturated fatty acids, vasodilators, vitamin B1 and some other substances.

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**INTRODUCTION**

Diabetes mellitus (DM) is a global epidemic affecting at least 8.3% of the population and 371 million people worldwide with a significant proportion (50%) remaining undiagnosed. It is estimated that almost one of six people are currently at risk of developing diabetes-related complications[1,2].

The majority of patients with long-term course of DM [mainly type 2 diabetes (T2DM)] are diagnosed with coronary heart disease (CHD) due to coronary vessels [arterial sclerotic disease](http://www.multitran.ru/c/m.exe?t=4856435_1_2&s1=%E0%F2%E5%F0%EE%F1%EA%EB%E5%F0%EE%F2%E8%F7%E5%F1%EA%EE%E5%20%EF%EE%F0%E0%E6%E5%ED%E8%E5). Often the course of CHD is complicated by combination of hypertension, specific kidney arterial involvement, eyes and lower limbs affection. Metabolic alterations in the myocardium are combined with early coronary atherosclerosis. All these changes in heart occur out of prolonged duration of DM among middle age and elderly patients [coronary vessels affection, myocardium changes, diabetic cardiac autonomic neuropathy (CAN) and [arterial sclerotic disease](http://www.multitran.ru/c/m.exe?t=4856435_1_2&s1=%E0%F2%E5%F0%EE%F1%EA%EB%E5%F0%EE%F2%E8%F7%E5%F1%EA%EE%E5%20%EF%EE%F0%E0%E6%E5%ED%E8%E5)] are associated with the term “diabetic heart or diabetic cardiomyopathy”. Conditionally, there are two main forms of heart disease in case of DM: diabetic cardiomyopathy (non-coronary genesis); ischemic heart disease. There is a metabolic stage (actual cardiomyopathy); metabolic-ischemic stage-ischemic heart disease; myocardial infarction (MI); dystrophic coronary cardiosclerosis; CAN[3-5].

Cardiac autonomic neuropathy among T2DM patients, is characterized by lesion of nerve fibers in the sympathetic and parasympathetic divisions of the autonomic nervous system, is diagnosed unsatisfactorily and may be accompanied by severe postural hypotension, decreased tolerance to the physical loadings, and cause the cardiac arrhythmias, ischemia of coronary vessels, “silent” MI, sudden death syndrome[6-9]. The aim of this study is to review the latest evidence and own data about the treatment perspectives of patients with DM and CAN.

**THERAPEUTIC APPROACHES FOR CAN**

Based on the CAN Subcommittee of the Toronto Consensus Panel on Diabetic Neuropathy[10], CAN is defined as the impairment of cardiovascular autonomic control among patients with established DM following the exclusion of other causes.

CAN in T2DM, which is characterized by lesion of nerve fibers in parasympathetic and sympathetic nervous systems, is one of the leading causes of heart arrhythmias and an independent risk factor for cardiovascular mortality among these patients[11,12]. CAN, especially at the early stages, can be subclinical and thus as the disease progresses, it becomes clinically evident.

Therefore, the problem of effective treatment of CAN is particularly relevant. Pathogenetic treatment of CAN includes: balanced diet and physical activity; optimization of glycemic control; treatment of dyslipoproteinemia (DLP); correction of metabolic abnormalities in myocardium; prevention and treatment of thrombosis; use of aldose reductase inhibitors (ARI); γ-linolenic acid, acetyl-L-carnitine, antioxidants, first of all α-lipoic acid (α-LA), use of long-chain ω-3 and ω-6 polyunsaturated fatty acids (ω-3 and ω-6 PUFAs), vasodilators, fat-soluble vitamin B1, aminoguanidine; substitutive therapy of growth factors and others[13-17].

It is obvious that the foreground should be therapy aimed at reducing insulin resistance (IR), correction of hyperglycemia, prevention and treatment of cardiomyopathy, symptomatic treatment of concomitant diseases and syndromes (hypertension, coronary artery disease, heart failure and arrhythmias)[18,19]. In this regard it is necessary to perform the following preventive and remedical therapy:

***Lifestyle modification***

Nutrition and physical activity. Correction of obesity. Limit salt intake to 2-4 g/d. Limit smoking, alcohol, foods that contain caffeine. It has been established that compliance with recommended lifestyle modifications (exercise, weight loss, *etc*.) help improve insulin sensitivity level. Sedentary lifestyle (less than 1000 kcal/wk) is accompanied by the risk of mortality three times higher than when living an active lifestyle. Dosed physical activity reduces hyperinsulinemia and encourages the tendency to normalize lipid metabolism in addition to body weight decrease. Physical activity is associated with higher heart rate variability (HRV) and lower heart rate, therefore may be a predictor of positive changes in HRV indices[20]. Obtaining the necessary amount of energy combined with physiologic food ration forms the dietary principles. The traditional Mediterranean diet (Greece and Southern Italy) is associated with longevity and/or low mortality due to cardiovascular disease (CVD) complications, decrease the incidence of T2DM, low frequency of wide range of chronic diseases, including rheumatoid arthritis, Parkinson's disease and others[21-23].

***Intensive glycemic control***

Compensation state of T2DM is recognized as a primary goal in the prevention of development and/or progression of CVD[2]. IR is a defining feature in most cases of T2DM and plays a key role in the pathogenesis of myocardial alternations. Obviously, pharmacological agents that are used in the treatment of diabetes should have positive qualities for correction of functional and structural disorders of the cardiovascular system[3,11,12].

Theoretically, pharmacological agents that improve insulin sensitivity [metformin*,* thiazolidinediones (TZD)] appear to be the most appropriate in this regard. It is established that metformin has a positive effect on glucose metabolism; Сa2+concentration in cardiomyocytes, but metformin, unlike TZD, does not show any positive effect on optimization of glucose metabolism in the myocardium[4,24]. TZD stimulate receptor transcription factors, activated by peroxisome proliferator activated receptor-γ (PPAR-γ), which improves insulin sensitivity and reduces the level of circulating free fatty acids (FFA). It is likely that TZD, despite the absence of the myocardium PPAR-γ type receptors, improve the functional state of the myocardium by reducing the content of FFA. However, the use of TZD among patients with CVD is limited due to the possibility of fluid retention and/or development of edema[25,26].

**Insulin and/or insulin** [**secretagogue**](http://www.multitran.ru/c/m.exe?t=4617987_1_2&s1=%F1%E5%EA%F0%E5%F2%E0%E3%EE%E3)**s:** Theoretically, their use may improve glucose metabolism in the myocardium and reduce the content of FFA, however, the assignment of these pharmacological agents is not conducive to the prevention of CVD in the experiment[4]. Inhibition of PPAR-α expression, which stimulates glucose metabolism and inhibit the metabolism of FFA’s, prevents the development of CVD in the experiment, and activation causes the formation of severe cardiomyopathy. Reduction of fat contents in nutrition among animals with increased expression of PPAR-α is accompanied by myocardium lesions warning, confirming the pathophysiological significance of activation of FFA metabolism. Similarly, the use of PPAR-γ agonist medications encourages the activation of glucose metabolism, inhibition of FFA metabolism, prevention of CVD[4].

**Glucagon-like peptide-1 medication:** Glucagon-like peptide-1 is one of the two leading “incretins” in the body-hormones that stimulate postprandial secretion and improve insulin sensitivity. The experiment established that the use of glucagon-like peptide-1 **(**GLP-1) improves the functional state of left ventriculum (LV) hemodynamic parameters[27]. However, GLP-1 medication can not be used in pharmacological therapy of CVD as under influence of [dipeptidyl peptidase](http://www.multitran.ru/c/m.exe?t=4602292_1_2&s1=%E4%E8%EF%E5%EF%F2%E8%E4%E8%EB%EF%E5%EF%F2%E8%E4%E0%E7%E0)-4 (DPP-4), GLP-1 is rapidly destroyed (effective half-life is only 1-2 min). Exenatideis 53% GLP-1 homologous and functions as a partial GLP-1 agonist receptor. Alternative to GLP-1 is the use of antagonists of DPP-4 (sitagiptin). However, the exenatide effectiveness as well as antagonists and DPP-4 in suspension/prevention of CVD in T2DM is not clear[27].

***Treatment of dyslipoproteinemia***

For DLP pharmacotherapy using statins, fibrates, bile acid sequestrants, nicotinic acid and its derivatives, products of long-chain ω-3 and ω-6 PUFA, or as an alternative-their combination with cholesterol absorption inhibitors[28].

**Statins:**Statins (along with lifestyle changes) should be prescribed to patients with T2DM aged over 40 where there is at least one of the risk factors for CVD (regardless of basic lipid levels); prescription of statins among patients with T2DM aged under 40 years without diagnosed CVD should be considered when low density lipoprotein (LDL) cholesterol level exceeds 2.6 mmol/L[29,30]. Achievment of LDL level in the blood < 1.8 mmol/L or reduction by 30%-40% compared with initial level (in case of failure to achieve value targets in the course of the prescription of the maximum tolerable dose statin) is suitable for patients at high risk of CVD, particularly patients with T2DM. However, statins are often ineffective when used for treatment of atherogenic DLP as pharmacological agents to achieve reduction in triglycerides (TG) and increase high density lipoprotein (HDL) cholesterol; statin use (even at high doses) only partially solves the problem of the risk of CVD[31-33].

**Fibrates:** Fibrateslimit the availability of substrates for the synthesis of TG in the liver, encourage lipoprotein lipase effects, increase LDL receptor/ligand interaction, stimulate cholesterol secretion with bile; stimulate reverse cholesterol transport, that is accompanied by reduction of TG and very low density lipoprotein (VLDL) cholesterol levels, and improve insulin sensitivity. Possible mechanisms that help fibrates improve insulin sensitivity are: fibrate binding to receptors that activate PPAR-β enhances fatty acids oxidation in the liver and, consequently, causes increase of insulin sensitivity; fibrates are involved in the regulation of adipokine expression [adiponectin, leptin, tumor necrosis-α (TNF-α), resistin *etc.*], accompanied by the increase of insulin sensitivity[34].

**Bile acid sequestrants**: Bile acid sequestrants are safe lipid-lowering medicaments, however often causing gastrointestinal adverse reactions. The second generation bile acid sequestrants, including сolesevelam binds bile acids with higher affinity and better tolerance. It is used as a supplement to diet therapy and physical activity to reduce the concentration of LDL cholesterol among patients with primary DLP, during monotherapy and/or in combination therapy with statins and to improve glycemic control among patients with T2DM. In addition, it is important that the bile acid sequestrants reduce the concentration of glucose and HbA1c in the blood (approximately 0.9%)[35] and thus may be useful in the treatment of hypercholesterolemia among patients with T2DM.

**Niacin:**Niacin is the most efficient pharmacological agent for raising HDL cholesterol level and, to a lesser extent, to reduce the concentration of TG and LDL cholesterol. It is reported that the therapeutic effect of prolonged forms of niacin on lipid profile occurs with the medicament intake in the dose range 0.5-2.0 g. A common reason for not using niacin, which significantly affects patien’s susception and accurate application is the problem of “flushing”. Current approach to this issue is the use of combined prolonged form of niacin with laropiprant, an inhibitor of prostaglandin D2[36,37].

**Long-chain ω-3 PUFAs:** The use of long-chain ω-3 PUFAs due to their effects on glucose homeostasis and IR (IR reduction in muscle > adipose tissue >> liver; presumably inhibit insulin secretion and delay the development of T2DM); influence on the state of lipid metabolism (decrease TG concentrations, presumably increase the concentration of HDL cholesterol, improve lipid profile among patients with T2DM and DLP); moderately reduce blood pressure (BP); improve endothelial function; reduce the inflammation and improve antioxidant protection[38-41].

**Ezetimibe:**Ezetimibe is used as a nutrition and exercise supplement to reduce the concentration of LDL cholesterol, total cholesterol (TC), and treatment of homozygous familial hypercholesterolemia. Despite some reservations, ezetimibe remains the medicine of first choice among other pharmacological agents in the absence of target specific level of LDL cholesterol using statin monotherapy[42].

**Combined treatment:** Therapy of first choice for T2DM in case of lipid profile correction is usage of statins to achieve specific target of LDL cholesterol level < 2.6 mmol/L for primary prevention and < 1.8 mmol/L for secondary prevention of CVD. Failure to get this target is the indication to combine statins with other lipid-lowering agents of other pharmacological groups. A number of international guidelines as a compulsory component of CVD risk monitoring recommend to control apolipoprotein B level on the first-priority basis. However, no results in multicentred, randomized, double-blind, placebo-controlled clinical trials makes it a therapeutic dilemma, since it is uncelar whether the intensification of statin therapy or combination of statins with fibrates and/or nicotinic acid will give the desired results[42,43].

***Correction of metabolic abnormalities in the myocardium***

Correction of metabolic abnormalities in the myocardium is the basis of pharmacotherapy that aims at optimization of the energy metabolism of the myocardium. Pharmacological impact system includes the following main aspects: use of metabolism regulators; energy-saving solutions; activators of endogenic high-energy compounds and O2 transportation; inhibitors of metabolic acidosis; membran protection: inhibition of lipid peroxidation membranes of cardiomyocytes; stabilization of lysosomal membranes, neutralization of membranotropic action of humoral agents of lysosomal proteases and others. Medicaments that enhance cell energy state (means of potential energy supply survival of ischemic myocardium). Deterioration of intracellular reserves of carbohydrates needs to be replenished by use of glycolysis activation measures. The use of macroergic phosphates (ATP, *etc*.) as a direct energy source is problematic, as the therapeutic effect of ATP in case of ischaemia, probably has less to do with disposing of its macroergic bonds but more with involving products of catabolism of ATP into energy metabolism of cardiomyocytes[4,44,45].

**Modulators of metabolism:** Insulin resistance affects myocardial function by reducing glucose transportation and oxidation of carbohydrates; enhancing the use of FFA; inhibition of Ca2+ transportation in the sarcolemma; violation of the structure and function of regulatory contractile proteins of myofibrils. In case of DM the reduction of myocardial energy formation leads to inhibition of glucose oxidation and preferential oxidation of fatty acids in the myocardium and skeletal muscle, which increases sensitivity to myocardial ischemia and leads to significant disturbances of Ca2+ homeostasis, deterioration of diastolic and systolic myocardial function. The presence of coronary artery disease (CAD) among patients with diabetes worsens the disease and significantly increases cardiovascular mortality. It is considered that even the initial stages of glycemic profile violations may influence the myocardial metabolism and contribute to the development of cardiomyopathy[4,44,45]. It is important that myocardial dysfunction is a suppositive stage of chronic hyperglycemia elaboration. Thus, dysfunction of cells metabolism, rather than systemic hyperglycemia is the reason for the elaboration of cardiac malfunction[4,46,47].

**Metabolic medicaments:**Optimization of myocardial energy metabolism is based on increased myocardial glucose oxidation, which enhances cardiac function and protects myocardial fibers from ischemic and reperfusion injuries. Myocardial use of glucose in case of chronic disease may be improved due to intake of the medicines, that can improve fatty acids metabolism and inhibit their oxidation. New therapeutic approach has been implemented after advent of trimetazidine-the first representative of a new class of metabolic agents- inhibitors of [3-ketoacyl coenzyme A thiolase](http://www.multitran.ru/c/m.exe?t=6239664_1_2&s1=3-%EA%E5%F2%EE%E0%F6%E8%EB-%EA%EE%FD%ED%E7%E8%EC-%C0%20%F2%E8%EE%EB%E0%E7%E0). Trimetazidine reduces oxidation of fatty acids; stimulates glucose intake; restores the link between glycolysis and carbohydrate oxidation, which leads to the formation of ATP, reducing O2 consumption; redirects fatty acids towards phospholipids; increases cell tolerance to ischemic and reperfusion injuries; increases the oxidation of glucose, the activity of Na+, K+-ATPase and Ca2+-pomps in the sarcoplasmic reticulum. Anti-ischemic properties of trimetazidine do not depend on changes in hemodynamics and are associated with a distinct recovery of mechanical function after ischemia, which makes it recognized as cardyo-cytoprotective agent. Trimetazidine prescription improves glucose metabolism; reduces endothelin-1 among patients with DCMP, that is taken to have effect on the vascular endothelium; accompanied by a significant positive changes in ejection fraction (EF) parameters among patients with heart failure; improves quality of life parameters and NYHA functional class[48,49]. Another pharmacological agent that facilitates the inhibition of metabolism of fatty acids is perhexiline*.* Perhexiline prescription to patients with heard failure significantly contributes to the improvement of EF, VO2max and quality of life. Unfortunately, the clinical use of this medicament is limited because of the risk of hepatotoxicity and peripheral neuropathy[50]. Ranolazine is the third antianginal pharmacological agent with a potential of metabolism modificator. However, the following factors do not allow to implement its use: the degree of inhibition of fatty acids metabolism is limited by physiological indicators; ranolazine prescription associates with the possibility of corrected QT (QTc) interval prolongation[51].

**Limitation of extracellular Ca2+ into the cell:**Blockers of Ca2+-channels show a protective effect on myocard in case of ischemia. In terms of correction of cell power the most pathogenetically efficient option is the use of Ca2+ blockers, however they only eliminate secondary dysfunction links of oxidative phosphorylation in mitochondria. Prescription of β-adrenergic receptor blockers for T2DM with CAD and CAN has significant pathogenetic grounds as high sympathetic activity that is followed by CAN, accelerate the development of CVD and significantly affects prognosis. In addition, several studies demonstrated the ability of β-blockers to reduce the incidence of “silent” myocardial ischemia episodes and improve prognosis among these patients. However, adrenergic receptors β-blockers negatively affect the performance of glycemic profile, increase the risk of hypoglycemia, showing a negative effect on blood lipid profile and can provoke acute heart failure. The above described events occur with prescription of non-selective β-blockers. Selective β-adrenergic receptor blockers, including metoprolol, are free of side effects, including the effectiveness of metoprolol in the treatment of CVD demonstrated in numerous controlled studies. Metoprolol has cardioprotective properties; improves prognosis among patients with CAD; has a fair tolerance in case of prolonged use. Cardioselective β-blockers can also balance the effects of autonomic dysfunction in particular by resisting sympathetic stimulation they can restore parasympathetic-sympathetic balance. However, traditional antianginal agents that affect hemodynamic parameters (β-blockers, Ca2+ antagonists, *etc*.), have lower tolerance among elderly due to the high risk of the interaction of pharmacological agents with a significant incidence of side effects[3,4,45,46].

**Medicaments that contain micro- and macroelements, primarily Mg2+:**One of the risk factors that can decrease insulin sensitivity is hypomagnesaemia. It is suggested that Mg2+ deficiency plays a significant role in increasing the risk of diabetic macro- and microvascular complications and, especially, risk of CAD[4,16,17].

***Thrombosis prevention and treatment***

Platelets obtained from patients with T2DM and tested in vitro are characterized by a real ability to aggregate under the influence of ADP, adrenaline, collagen, arachidonic acid, and thrombin. Aggregation of platelets is significantly increased in the second, irreversible phase, which depends on the transformation of arachidonic acid into labile prostacyclin and thromboxane. Thus, the possibility of ADP receptors of platelet membranes blocking is a pathogenetically justified measure. Prescription of antiplatelet agents, namely acetylsalicylic acid (ASA), clopidogrel and others can help prevent blood clots, stenocardia and development of MI. The active clopidogrel metabolite irreversibly binds to ADP receptor on the platelet membrane, which leads to inhibition of adenylate cyclase; inhibition of ADP-dependent secretion of platelet granules; inhibition of ADP-dependent process of binding fibrinogen receptor to the platelet membrane; does not affect the expression of receptors directly; blocks myointymal proliferation in case of vascular damage; unlike ASA does not affect the activity of cyclooxygenase. Effect of clopidogrel and ASA synergy is demonstrated in the study of platelet *ex vivo*. However, clopidogrel is more effective pharmacological agent within the frames of the combined risk of MI, stroke, and the syndrome of “sudden death” reduction[52-55].

***Aldose reductase inhibitors***

ARI inhibit the glucose polyol way metabolism, prevent the reduction of the redox potentials. Analysis of the double-blind, placebo-controlled study established that tolrestat contributes to the improvement of independent tests results and vibration sensitivity among patients with symmetric diabetic peripheral neuropathy (DPN). Zenarestat prescription for 12 mo was accompanied by a dose-dependent changes in the spissitude of nerve tissue, increased the velocity of nerve impulses, improved myocard systolic function. Zoporestat, ranirestat-medicaments of a new generation of ARI group showed sufficient efficacy in experimental studies[56-59].

***Replacement therapy with help of myoinositol***

Several individual clinical trials were conducted for the study of myoinositol efficacy in the treatment of diabetic neuropathy. The results are quite positive, but the future clinical double-blind, placebo-controlled trials are needed [60-62].

***Aminoguanidine***

Aminoguanidine improves capacity of nerve velocity, increases blood flow, inhibits the formation of a[dvanced glycation endproduct](http://www.multitran.ru/c/m.exe?t=4851577_1_2&s1=%EA%EE%ED%E5%F7%ED%FB%E9%20%EF%F0%EE%E4%F3%EA%F2%20%E3%EB%E8%EA%E8%F0%EE%E2%E0%ED%E8%FF)s, delays the emergence and development of albuminuria. Analysis of controlled trials confirmed quite aminoguanidine high efficiency among patients with diabetic neuropathy, but the development of a number of side effects terminated their application. The use of aminoguanidine derivatives is accompanied byclinical efficacy and lack of adverse side effects[6,8,11]. The results are promising, but need further clinical double-blind, placebo-controlled studies.

***Neurotrophic therapy***

Inhibition of nerve growth factor (NGF) expression and its receptors suppresses NGF axonal retrograding transport and reduces the activity of small demyelinamted neurons and their neuropeptides, including substance P and gene-linked calcitonin peptide. The use of recombinant human NGF normalizes neuropeptide concentration and prevents the development of sensory neuropathy in the experiment. However, the results of clinical placebo-controlled studies deny the positive impact of recombinant human NGF among patients with diabetic neuropathy[6,8].

***Antineural autoimmunity. Human immunoglobulin for intravenous use***

Intravenous human immunoglobulin prescription is recommended for patients with DPN, which have signs of antineural autoimmunity symptomes. The side effects include headache, and the main danger could be the development of an anaphylactic reaction, however, it affects mainly patients with deficiency of immunoglobulin A[6,8].

***Endoneural perfusion inhibition with the development of hypoxia***

Experimental and clinical studies have shown benefit in the efficiency of vasodilators when used for improvement of nerve flow velocity, but there is not enough information about the impact of vasodilators on the course of DPN during clinical double-blind placebo-controlled studies. The research results of characteristics that impact the ACE inhibitors on heart rate variability parameters among diabetic patients with CAN appeared to show diametrically opposed results. In particular, prescription of quinapril for 3 mo was accompanied by statistically significant increased parasympathetic activity, and the use of trandolaprilfor 12 mo did not affect the performance of autonomic myocardial function. However, most of these pharmacological agents have no proven clinical and electrophysiological positive effects and have certain limitations and contraindications[4,5,6,11].

***Activation of free radical stress***

Considering that one of the major pathogenetic mechanisms of neuropathy is oxidative stress (OS), the need for antioxidants prescription is obvious. Great therapeutic potential is observed in α-LA and creates pathogenic evidence for the use of this pharmacological agent[63-65]. Mechanism of α-LA action is not fully developed, but specific attention should be paid to two hypotheses. Firstly, α-LA phenomenon causes dose-dependent proliferation of neuroblastoma cultured cells. Changes in the membrane fluidity that are mediated through sulfhydryl groups α-LA are considered to cause this effect. This is confirmed by the following results of several studies, including experimental neuropathy induced by acrylamide, followed by a significant inhibition of proliferation of the above phenomenon; overlay and/or progression of experimental distal neuropathy, mainly caused by a decrease of content of substances in axons containing sulfhydryl groups (*e.g.*, glutathione); α-LA *in vivo* and *in vitro* enhances spontaneous processes of expansion and improvement of the structural and functional nerve terminals membranes state; prescription of α-LA stimulates the regeneration of nerve terminals in case of the partial denervation, as well as experimental hexacarbon neuropathy. Secondly, and the most probable mechanism is the ability of α-LA to function as a radical binder (“cleaner”)[66-69].

***Vitamins with antioxidant properties [(a liposoluble vitamin B1 (benfotiamin)], combined medications***

There is enough experimental and clinical results of studies that suggest that the hyperinsulinemia, IR, and chronic hyperglycemia in T2DM have a negative impact on the metabolism of thiamine particularly due to the inhibition of the functional state of the thiamine transporter-1 and thiamine transporter-2, responsible for the reabsorbation of vitamin in the proximal tubules of the kidneys; transketolase activity, which can lead to the congestion of intermediates in the initial stages of glycolysis [glyceraldehyde-3-phosphate (GA3P), fructose-6-phosphate (F6P) and dihydroxyacetone-phosphate]. Congestion of intermediates in case of chronic hyperglycemia increases the production of free radicals in the mitochondria, followed by inhibition of glyceraldehyde-3-phosphate dehydrogenase (GAPDH). Increased concentrations of GA3P, F6P and GAPDH can initiate induced hyperglycemia, metabolic fates that favor the overlay of vascular injury, including activation of proteinkinase-C, accumulation of advanced glycation end products (AGEs) hexosamine biosynthetic fates activation, dicarbonyl compounds. Activation with dicarbonyl compounds is followed by further stimulation of the AGEs formation, which is also associated with functional impaired and structural state of cardiomyocytes[70-72].

It is clear that the correction of thiamin deficiency must be performed using exogenous vitamin B1*,* or benfotiamin(monophosphate S-benzoyl-thiamine, high-bioavailable liposoluble vitamin B1 derivatives). Results of experimental and clinical studies suggest a positive effect of benfotiamin prescription on prevention of diabetic vascular disease progression. Benfotiamin broad therapeutic potential has a good efficiency on medications containing soluble thiamine derivatives for the purpose of regulating the activity of free radical processes; correction of endothelial dysfunction in case of CVD, stabilization of clinical and antioxidant effects. Benfotiamin favoring the transketolase (TK) activity prevents the activation of pathophysiological mechanisms by reorientation towards of F6P and GAPDH metabolism[73-75]. Benfotiamin can promote neuronal and vascular deficiency correction through participation of NO processes, which have a significant therapeutic potential for the treatment of СVD. The use of thiamine and α-LA combination has a great significance in the treatment of diabetic angio-neuropathy. In particular, it demonstrated that prescription of benfotiamin and α-LA to patients with type 1 DM was followed by normalization of hyperglycemia and for 4 wk it promoted the normalization of prostacyclin synthase suppressed by diabetes; increase of TK activity in monocytes in 2-3 times[76-80].

***Fatty acids metabolism disorders ( γ-Linolenic acid, acetyl L-Carnitine)***

Vasoactive prostanoids, metabolites and dihomo-γ-linolenic acid (DGLA), including prostaglandins and other eicosanoids are necessary for the physiological behavior of nerve conductivity and blood flow. The results of double-blind, placebo-controlled studies showed that prescription of DGLA to patients with DPN is followed by positive dynamics in clinical course, as well as increase in the speed of nerve conductivity. L-carnitine’s main function is to strengthen the metabolism of fatty acids, but there are experimental evidence of L-carnitine’s ability to activate glucose metabolism. It is believed that T2DM is characterized by malfunction of L-carnitine exchange in the mitochondria. The results of several studies showed that prescription of L-carnitine helps to improve energy supplies and LV function. It is established that propionyl-L-carnitine improves the functional status, used as glucose energy oxidation in the rat’s affected myocardium (despite the increased level of fatty acids). Nutrition of diabetic mice with obesity with L-carnitine addition increases the level of acyl-carnitine in the blood, muscle, liver and adipose tissue; increases levels of piruvate dehydrogenase activity in the muscles; prescription of zinc-carnitine mixture reduces hyperglycemia and improves glucose tolerance. L-carnitine infusion with the help of hyperinsulinemic-euglycemic clamp improves glusoce profile control, reduces the concentration of circulating lipids. L-carnitine prescription for 3 or 6 mo for newly diagnosed patients with T2DM with lipid metabolism disorders is followed by a statistically significant decrease in lipoprotein(a) [Lp(a)] levels. The results of double-blind, placebo-controlled studies among patients with verified hyperLP(a) established that L-carnitine (2 g/d) encouraged a significant decrease in the concentration of Lp(a) levels; L-carnitine incorporation into nutrition of patients with newly diagnosed T2DM is followed by similar changes; combined L-carnitine with simvastatin (20 mg/d) treatment is much more efficient in decreasing the concentration of lipids, including TG and Lp(a) than statin monotherapy. Thus, L-carnitine can be used as one of the components for lipid-modifying therapy among patients with T2DM[81,82].

***ω-3 and ω-6 PUFAs medications***

A fundamentally new approach to assessing the biological role of eicosapentaenoic (EPA) and docosahexaenoic acid (DHA) is associated with long-term epidemiological studies results among Inuits, which established a small percentage of CVD. The Greenlandic Inuits were observed to have an increased bleeding duration, lower levels of TC, TG, VLDL-cholesterol and a significant increase in TC lipid membranes of EPA and DHA contents, arachidonic acid concentration reduction and linoleic acid. For the first time these results allowed to express a reasonable assumption about the protective effect of DHA and especially EPA from the damaging effects on the internal vessel wall cause capable of inducing experiment CAD-a phenomenon of TC activation and high blood viscosity, enhanced the cyclicendoperoxide synthase, including prostaglandin H2, TXA2 activation of endothelial cell proliferation, hypercholesterolemia and hypertriglyceridemia. Prescription of EPA and DHA is followed by a decrease in the “rigidity” of red blood cells, which is obviously associated with labilization of erythrocyte plasmolemma based on rapid and intensive incorporation of long-chain ω-3 PUFA phospholipids into membrane and decreased synthesis of vasoconstrictor active ingredients. The ability of exogenous EPA and DHA to incorporate phospholipid blood cell membranes and membrane phospholipids of endothelial cells blood vessels affects the fundamental plasmolemma properties and receptors function for the perception and processing of extracellular information. Accumulating long-chain polyenes acids, labilize plasmolemma, changing the microviscosity of its lipid matrix, which causes the transformation of the basic plasmolemma properties-permeability, generation of biopotentials, ions transit. Changes in the lipid environment of receptor structures affects their functional activity and enzyme systems control in the cell, which primarily relates to the corpuscular adenylate cyclase, whose function is related to the metabolism of phospholipids[83-85].

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 IR in experimental diabetes, decrease level of BP, dose-dependently prevent the development of diabetes, improve the sensitivity of platelets to ADP and collagen, contribute to positive changes in the parameters of coagulation, endothelial cells migration, inhibitsthe proliferation of smooth muscle cells. However, the studies aimed to investigate the features of omega-3 PUFA in T2DM are numerically small and obtained results do not always testify to their effectiveness[86-93]. In particular, the results of the ORIGIN trial demonstrated, that administration of 1 g ω-3 PUFA did not reduce the rate of death caused by cardiovascular reasons or their outcomes during a period of 6 years among 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. However, this study did not apply to treatment of CAN and it was decided to continue the study for a few more years[94]. In the same time, American Diabetes Association (ADA, 2005) recommend the prescription of α-LA and ω-3 PUFA in algorithms of DPN treatment[95] and in ADA recommendations (2014) and results of some trials–prescription of ω-3 PUFA in DLP treatment among patients with T2DM and cardiovascular diseases[2,90,91,92].

To explore the effectiveness of some above-mentioned compounds we examined 81 patients with T2DM and CAN, patients were aged between 50-59 years with disease duration 1-6 years and median HbA1c 7.1 ± 0.4%. CAN was diagnosed according to previously proposed criteria[8,10,12]. 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 allocated to five treatment groups: first group received traditional antihyperglycemic therapy (*n* = 15, control group); patients in group 2 (*n* = 21), received in addition to standard treatment 1 capsule/d of the ω-3 PUFA; patients in 3rd group (*n* = 12) –benfotiamine 300 mg/d; patients in 4th group (*n* = 18) –600 mg of α-LA, patients in 5th (*n* = 15) –1 capsule/d of the ω-3 PUFA, benfotiamine 300 mg/d and 600 mg of α-LA. Each one gram capsule of the ω-3 PUFA contains approximately 465 mg of EPA and 375 mg of DHA. The duration of the treatment was three months.

The concentration of glucose in the blood was determined by the glucose oxidase method while HbA1c was assessed by using a highly sensitive method of ion-exchange liquid chromatography with D-10 analyzer and BIO-RAD reagents (USA). Determination of immunoreactive insulin (IRI) was performed using commercial kits from Immunotech Insulin IRMA reagents (Czech Republic); leptin level-from Immunotech Leptin (Czech Republic) test kits; TNF-α–from Vector-Best (Russia); high-sensitivity C-reactive protein (hsCRP)–from DRG (USA); N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP)-from Biomedica (Austria) kits and an ELISA analysis technique. Lipid metabolism was assessed by the concentration of TC, LDL-, HDL-, VLDL-cholesterol measurments. The lipid fractions were determined by using HUMAN reagents (Germany) for the analyzer HUMANLAYZER 2000.

We found out 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 among 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 lead to a significant decrease of the NT-proBNP level [-6.8 ± 1.1%, (*P* < 0.05)] compared to the control group. Сhanges of NT-proBNP and lipid metabolism parameters among patients with T2DM and CAN after 3-months of ω-3 PUFA therapy are given in Table 1.

Benfotiamin prescription to patients with T2DM and CAN did not cause any significant changes in lipid profile and leptin levels (*P* > 0.05), while it probably helped reduce the IRI concentration [-12.7 ± 1.4%, (*P* < 0.05)]. The use of benfotiamin in the comprehensive treatment of T2DM helped reducing hsCRP [-13.3 ± 2.1%, (*P* < 0.05)] and TNF-α [-10.2 ± 1.6%, (*P* < 0.05)] concentrations, but the prescription of α-LA was followed by a significant decrease in these parameters [-15.2 ± 1.9%, (*P* < 0.01) and -14.7 ± 1.8%, (*P* < 0.001), accordintly] and facilitated visible LDL cholesterol [-14.2 ± 1.8%, (*P* < 0.05)], IRI [-15.9 ± 1.6%, (*P* < 0.01)] and leptin [-16.3 ± 1.2, (*P* < 0.001)] reduction, also increased [HDL cholesterol](http://www.multitran.ru/c/m.exe?t=4349830_1_2&s1=%F5%EE%EB%E5%F1%F2%E5%F0%E8%ED%20%EB%E8%EF%EE%EF%F0%EE%F2%E5%E8%ED%EE%E2%20%E2%FB%F1%EE%EA%EE%E9%20%EF%EB%EE%F2%ED%EE%F1%F2%E8) level [+7.8 ± 0.7%, (*P* < 0.01)]. Combined ω-3 PUFA, benfotiamin and α-LA prescription was followed by the more pronounced decrease of IRI, leptin and some inflammation factors (Table 2).

Obtained results of this study could prove that prescription of ω-3 PUFA is accompanied by more significant decrease of TG and increase of HDL cholesterol levels compared to patients in control group. The complex therapy with α-LA contributes to more evident antiatherogenic effect, in particular decrease of LDL and TC, increase of HDL cholesterol level (compared to patients of 1st, 2nd and 3rd groups). Combined prescription of ω-3 PUFA, benfotiamine and α-LA is followed by more statistically significant positive changes of lipid profile (Table 3).

In order to evaluate the artery stiffness parameters during active and passive periods of the day the 24-h blood pressure profile, aortha (AIxao) and brachial augmentation index (AIxbr), pulse wave velocity (PWV) and ambulatory arterial stiffness index (AASI) were assessed by TensioMedTM Arteriograph 24 (Hungary). The program orders the values of the AIxbr and PWV into ranges as follows: optimal values: AIxbr > -30%, PWV < 7 m/s; normal values: -30% < AIxbr < -10%, 7 m/s < PWV < 10 m/s; elevated values: -10% < AIxbr < 9.8%, 9.8 m/s < PWV < 12 m/s; pathological values: AIxbr > 10%, PWV > 12 m/s[96]. The study involved 51 patients with T2DM, among them 12 patients without CVD and CAN, 39 patients with moderate CAN. Patients with diagnosed CAN were allocated to two groups: control group (*n* = 18) received traditional antihyperglycemic therapy and treatment group (*n* = 21) received in addition to standard treatment 1 capsule/d of the ω-3 PUFA. Control–12 healthy volunteers. Artery stiffness parameters among patients with T2DM without CAN were within normal limits, but this group has a tendency toward increase of vascular wall stiffness parameters. The arterial stiffness parameters among patients with moderate CAN exceed the physiological values, in particular AIxao +26.2% (*P* < 0.01), AIxbr +66.2% (*P* < 0.001), PWV +24.7% (*P* < 0.001), AASI +30.6% (*P* < 0.01) compared to patients with T2DM without CAN and were considered as high (Table 4). After 1.5 mo of treatment we found out that there was a decrease of AIxbr (-10.0 ± 2.62%, *P* < 0.05) and PWV (9.8 ± 0.42 m/s, *P* < 0.01) values in treatment group. Prescription of ω-3 PUFA for three months was followed by more significant decrease of AIxao (27.8 ± 1.13%, *P* < 0.05), PWV (9.3 ± 0.42, m/s, *P* < 0.01) during the 24 h; decrease of AIxao (16.2 ± 3.12%, *P*< 0.01), PWV (-11.6 ± 2.09%, *P* < 0.05) during the day and decrease of AIxao (-11.2 ± 4.2%, *P* < 0.05), AIxbr (-98.0 ± 18.1%, *P* < 0.05), PWV (-18.9 ± 3.9%, *P* < 0.01) during the night. At the same time there wasn’t significant influence on the AIxbr during the active period of day (Table 5 and 6). Therefore, the administration of ω-3 PUFA to patients with T2DM for three months promotes arterial stiffness parameters improvement.

We previously reported that the use of ω-3 PUFA, 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. Thus, prescription of ω-3 PUFA contributed to 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 followed by a tendency to a low pulse pressure[97-101]. The influence of ω-3 PUFA on the dynamics of metabolism is probably caused by 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. The combination of the positive influences of ω-3 PUFA on NT-proBNP, lipid profile and their moderate hypotensive effects 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 among patients with T2DM and CAN are necessary[102-104].

***Orthostatic hypotension treatment***

Postural hypotension syndrome is manifested by dizziness and possibility of consciousness loss. Hypovolemia and sympathoadrenal disorders are the most characteristic features among patients with T2DM and orthostatic hypotension. Postural hypotension among most diabetic patients progresses asymptomatically and, therefore, does not require correction. However, in severe cases–it is key traumatic factor. Treatment of symptomatic postural hypotension among patients with CAN is very complicated because of the need to achieve a balance between changes in BP in the vertical and horizontal position. The increase of peripheral venous inflow is achieved through the use of elastic tightening body linen. It is inappropriate to prescribe psychotropic and diuretic drugs, and eliminate the possibility of electrolyte disorders and/or reduce the fluid volume. Prescription of glucocorticoids is efficient among some patients with postural hypotension, but may be followed by the development of edema, risk of arterial hypertention.Metoclopramide is effecient among patients with excessive dopaminergic activity, or increased sensitivity to dopaminergic stimulation. The ineffectiveness of the above remedial measures requires the prescription of α1-adrenergic agonists (midodrine) or dihydroergotamine combined with caffeine. Exceptional refractory to the treatment, often postprandial orthostatic hypotension forms determine the necessity of octreotidum prescription[105,106].

**PROSPECTIVE DIRECTIONS OF CAN TREATMENT**

The revival of interest in vascular hypothesis of CAN, OS index, neurotrophic hypothesis and importance of autoimmune disorders opens up new areas of treatment. The promising methods include research and use of tools that increase blood flow through the vasa vasorum, including butaprost (prostacyclin analogue), TXA2 blockers and drugs that contribute into strengthening and/or normalization of Na+, K+-ATPase (cilostazol- a potential [phosphodiesterase](http://www.multitran.ru/c/m.exe?t=492272_1_2&s1=%F4%EE%F1%F4%EE%E4%E8%FD%F1%F2%E5%F0%E0%E7%E0) inhibitor), α-LA, DGLA, ω-3 PUFAs, and the simultaneous prescription of α-LA, ω-3 PUFA and DGLA[107-112]. In addition, the combination of α-LA, ω-3 PUFAs, DGLA and ARI is the most rational pathogenetically justified use.

**REFERENCES**

1 Federation ID. IDF Diabetes Atlas 2012 Update. 2012. Available from: URL: http //www.idf.org/diabetesatlas/5e/Update2012

2 [**American Diabetes Association**](http://www.ncbi.nlm.nih.gov/pubmed/?term=American%20Diabetes%20Association%5BCorporate%20Author%5D). Standards of medical care in diabetes--2014. *Diabetes Care* 2014; **37** Suppl 1: S14-S80 [PMID: 24357209 DOI: 10.2337/dc14-S014]

3 **Marazzi G**, Volterrani M, Rosano GM. Metabolic agents in the management of diabetic coronary patients: a new era. *Int J Cardiol* 2008; **127**: 124-125 [PMID: 18199501 DOI: 10.1016/j.ijcard.2007.10.042]

4 **Witteles RM**, Fowler MB. Insulin-resistant cardiomyopathy clinical evidence, mechanisms, and treatment options. *J Am Coll Cardiol* 2008; **51**: 93-102 [PMID: 18191731 DOI: 10.1016/j.jacc.2007.10.021]

5 **Rutter MK**, Nesto RW. Blood pressure, lipids and glucose in type 2 diabetes: how low should we go? Re-discovering personalized care. *Eur Heart J* 2011; **32**: 2247-2255 [PMID: 21705358 DOI: 10.1093/eurheartj/ehr154]

6 **Maser RE**, Lenhard MJ. Cardiovascular autonomic neuropathy due to diabetes mellitus: clinical manifestations, consequences, and treatment. *J Clin Endocrinol Metab* 2005; **90**: 5896-5903 [PMID: 16014401 DOI: 10.1210/jc.2005-0754]

7 **Spallone V**, Ziegler D, Freeman R, Bernardi L, Frontoni S, Pop-Busui R, Stevens M, Kempler P, Hilsted J, Tesfaye S, Low P, Valensi P. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. *Diabetes Metab Res Rev* 2011; **27**: 639-653 [PMID: 21695768 DOI: 10.1002/dmrr.1239]

8 **Callaghan BC**, Cheng HT, Stables CL, Smith AL, Feldman EL. Diabetic neuropathy: clinical manifestations and current treatments. *Lancet Neurol* 2012; **11**: 521-534 [PMID: 22608666 DOI: 10.1016/S1474-4422(12)70065-0]

9 **Dimitropoulos G**, Tahrani AA, Stevens MJ. Cardiac autonomic neuropathy in patients with diabetes mellitus. *World J Diabetes* 2014; **5**: 17-39 [PMID: 24567799 DOI: 10.4239/wjd.v5.i1.17]

10 **Tesfaye S**, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, Lauria G, Malik RA, Spallone V, Vinik A, Bernardi L, Valensi P. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care* 2010; **33**: 2285-2293 [PMID: 20876709 DOI: 10.2337/dc10-1303]

11 **Vinik AI**, Ziegler D. Diabetic cardiovascular autonomic neuropathy. *Circulation* 2007; **115**: 387-397 [PMID: 17242296 DOI: 10.1161/CIRCULATIONAHA.106.634949]

12 **Vinik AI**, Erbas T. Diabetic autonomic neuropathy. *Handb Clin Neurol* 2013; **117**: 279-294 [PMID: 24095132 DOI: 10.1016/B978-0-444-53491-0.00022-5]

13 **Edwards JL**, Vincent AM, Cheng HT, Feldman EL. Diabetic neuropathy: mechanisms to management. *Pharmacol Ther* 2008; **120**: 1-34 [PMID: 18616962 DOI: 10.1016/j.pharmthera.2008.05.005]

14 **Cannon CP**. Combination therapy in the management of mixed dyslipidaemia. *J Intern Med* 2008; **263**: 353-365 [PMID: 18324928 DOI: 10.1111/j.1365-2796.2008.01933.x]

15 **Bril V**. Treatments for diabetic neuropathy. *J Peripher Nerv Syst* 2012; **17** Suppl 2: 22-27 [PMID: 22548619 DOI: 10.1111/j.1529-8027.2012.00391.x]

16 **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**: 7-22 [PMID: 22217193 DOI: 10.2165/11594650-000000000-00000]

17 **Hosseini A**, Abdollahi M. Diabetic neuropathy and oxidative stress: therapeutic perspectives. *Oxid Med Cell Longev* 2013; **2013**: 168039 [PMID: 23738033 DOI: 10.1155/2013/168039]

18 **Vinik AI**, Maser RE, Ziegler D. Neuropathy: the crystal ball for cardiovascular disease? *Diabetes Care* 2010; **33**: 1688-1690 [PMID: 20587730 DOI: 10.2337/dc10-0745]

19 **Vinik AI**, Nevoret ML, Casellini C, Parson H. Diabetic neuropathy. *Endocrinol Metab Clin North Am* 2013; **42**: 747-787 [PMID: 24286949 DOI: 10.1016/j.ecl.2013.06.001]

20 **Soares-Miranda L**, Sandercock G, Vale S, Santos R, Abreu S, Moreira C, Mota J. Metabolic syndrome, physical activity and cardiac autonomic function. *Diabetes Metab Res Rev* 2012; **28**: 363-369 [PMID: 22238216 DOI: 10.1002/dmrr.2281]

21 **Maser RE**, Lenhard MJ. An overview of the effect of weight loss on cardiovascular autonomic function. *Curr Diabetes Rev* 2007; **3**: 204-211 [PMID: 18220673 DOI: 10.2174/157339907781368931]

22 **Derosa G**, Limas CP, Macías PC, Estrella A, Maffioli P. Dietary and nutraceutical approach to type 2 diabetes. *Arch Med Sci* 2014; **10**: 336-344 [PMID: 24904670 DOI: 10.5114/aoms.2014.42587]

23 **Vincent AM**, Calabek B, Roberts L, Feldman EL. Biology of diabetic neuropathy. *Handb Clin Neurol* 2013; **115**: 591-606 [PMID: 23931804 DOI: 10.1016/B978-0-444-52902-2.00034-5]

24 **Home PD**, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJ. Rosiglitazone evaluated for cardiovascular outcomes--an interim analysis. *N Engl J Med* 2007; **357**: 28-38 [PMID: 17551159 DOI: 10.1056/NEJMoa073394]

25 **Valensi P**, Extramiana F, Lange C, Cailleau M, Haggui A, Maison Blanche P, Tichet J, Balkau B. Influence of blood glucose on heart rate and cardiac autonomic function. The DESIR study. *Diabet Med* 2011; **28**: 440-449 [PMID: 21204961 DOI: 10.1111/j.1464-5491.2010.03222.x]

26 **Nissen SE**, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007; **356**: 2457-2471 [PMID: 17517853 DOI: 10.1056/NEJMoa072761]

27 **Salehi M**, D'Alessio DA. New therapies for type 2 diabetes based on glucagon-like peptide 1. *Cleve Clin J Med* 2006; **73**: 382-389 [PMID: 16610399 DOI: 10.3949/ccjm.73.4.382]

28 **Wanders D**, Plaisance EP, Judd RL. Pharmacological effects of lipid-lowering drugs on circulating adipokines. *World J Diabetes* 2010; **1**: 116-128 [PMID: 21537437 DOI: 10.4239/wjd.v1.i4.116]

29 **Ascaso JF**. [Advances in cholesterol-lowering interventions]. *Endocrinol Nutr* 2010; **57**: 210-219 [PMID: 20451478 DOI: 10.1016/j.endonu.2010.03.008]

30 **Martinez-Hervas S**, Carmena R, Ascaso JF. Significance of LDL-C lowering therapy in diabetic patients. *Clin Lipidology* 2011; **6**: 389-399 [DOI: 10.2217/clp.11.28]

31 **Blum A**, Shamburek R. The pleiotropic effects of statins on endothelial function, vascular inflammation, immunomodulation and thrombogenesis. *Atherosclerosis* 2009; **203**: 325-330 [PMID: 18834985 DOI: 10.1016/j.atherosclerosis.2008.08.022]

32 **Stanley WC**, Recchia FA, Lopaschuk GD. Myocardial substrate metabolism in the normal and failing heart. *Physiol Rev* 2005; **85**: 1093-1129 [PMID: 15987803 DOI: 10.1152/physrev.00006.2004]

33 **Devaraj S**, Siegel D, Jialal I. Simvastatin (40 mg/day), adiponectin levels, and insulin sensitivity in subjects with the metabolic syndrome. *Am J Cardiol* 2007; **100**: 1397-1399 [PMID: 17950796 DOI: 10.1016/j.amjcard.2007.06.028]

34 **Belfort R**, Berria R, Cornell J, Cusi K. Fenofibrate reduces systemic inflammation markers independent of its effects on lipid and glucose metabolism in patients with the metabolic syndrome. *J Clin Endocrinol Metab* 2010; **95**: 829-836 [PMID: 20061429 DOI: 10.1210/jc.2009-1487]

35 **Staels B**, Kuipers F. Bile acid sequestrants and the treatment of type 2 diabetes mellitus. *Drugs* 2007; **67**: 1383-1392 [PMID: 17600387 DOI: 10.2165/00003495-200767100-00001]

36 [**AIM-HIGH Investigators**](http://www.ncbi.nlm.nih.gov/pubmed/?term=AIM-HIGH%20Investigators%5BCorporate%20Author%5D). The role of niacin in raising high-density lipoprotein cholesterol to reduce cardiovascular events in patients with atherosclerotic cardiovascular disease and optimally treated low-density lipoprotein cholesterol: baseline characteristics of study participants. The Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: impact on Global Health outcomes (AIM-HIGH) trial. *Am Heart J* 2011; **161**: 538-543 [PMID: 21392609 DOI: 10.1016/j.ahj.2010.12.007]

37 **Cefali EA**, Simmons PD, Stanek EJ, Shamp TR. Improved control of niacin-induced flushing using an optimized once-daily, extended-release niacin formulation. *Int J Clin Pharmacol Ther* 2006; **44**: 633-640 [PMID: 17190373 DOI: 10.5414/CPP44633]

38 **Carpentier YA**, Portois L, Malaisse WJ. n-3 fatty acids and the metabolic syndrome. *Am J Clin Nutr* 2006; **83**: 1499S-1504S [PMID: 16841860]

39 **von Schacky C**, Harris WS. Cardiovascular benefits of omega-3 fatty acids. *Cardiovasc Res* 2007; **73**: 310-315 [PMID: 16979604 DOI: 10.1016/j.cardiores.2006.08.019]

40 **von Schacky C**. Omega-3 fatty acids: antiarrhythmic, proarrhythmic or both? *Curr Opin Clin Nutr Metab Care* 2008; **11**: 94-99 [PMID: 18301082 DOI: 10.1097/MCO.0b013e3282f44bdf]

41 **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**: 413-428 [PMID: 19422375 DOI: 10.1111/j.1476-5381.2009.00189.x]

42 **Fleg JL**, Mete M, Howard BV, Umans JG, Roman MJ, Ratner RE, Silverman A, Galloway JM, Henderson JA, Weir MR, Wilson C, Stylianou M, Howard WJ. Effect of statins alone versus statins plus ezetimibe on carotid atherosclerosis in type 2 diabetes: the SANDS (Stop Atherosclerosis in Native Diabetics Study) trial. *J Am Coll Cardiol* 2008; **52**: 2198-2205 [PMID: 19095139 DOI: 10.1016/j.jacc.2008.10.031]

43 **Tomassini JE**, Mazzone T, Goldberg RB, Guyton JR, Weinstock RS, Polis A, Jensen E, Tershakovec AM. Effect of ezetimibe/simvastatin compared with atorvastatin on lipoprotein subclasses in patients with type 2 diabetes and hypercholesterolaemia. *Diabetes Obes Metab* 2009; **11**: 855-864 [PMID: 19508464 DOI: 10.1111/j.1463-1326.2009.01061.x]

44 **Morisco C**, Condorelli G, Trimarco V, Bellis A, Marrone C, Condorelli G, Sadoshima J, Trimarco B. Akt mediates the cross-talk between beta-adrenergic and insulin receptors in neonatal cardiomyocytes. *Circ Res* 2005; **96**: 180-188 [PMID: 15591229 DOI: 10.1161/01.RES.0000152968.71868.c3]

45 **Nikolaidis LA**, Poornima I, Parikh P, Magovern M, Shen YT, Shannon RP. The effects of combined versus selective adrenergic blockade on left ventricular and systemic hemodynamics, myocardial substrate preference, and regional perfusion in conscious dogs with dilated cardiomyopathy. *J Am Coll Cardiol* 2006; **47**: 1871-1881 [PMID: 16682315 DOI: 10.1016/j.jacc.2005.11.082]

46 **Sytze Van Dam P**, Cotter MA, Bravenboer B, Cameron NE. Pathogenesis of diabetic neuropathy: focus on neurovascular mechanisms. *Eur J Pharmacol* 2013; **719**: 180-186 [PMID: 23872412 DOI: 10.1016/j.ejphar.2013.07.017]

47 **Yagihashi S**, Mizukami H, Sugimoto K. Mechanism of diabetic neuropathy: Where are we now and where to go? *J Diabetes Investig* 2011; **2**: 18-32 [PMID: 24843457 DOI: 10.1111/j.2040-1124.2010.00070.x]

48 **Fragasso G**, Palloshi A, Puccetti P, Silipigni C, Rossodivita A, Pala M, Calori G, Alfieri O, Margonato A. A randomized clinical trial of trimetazidine, a partial free fatty acid oxidation inhibitor, in patients with heart failure. *J Am Coll Cardiol* 2006; **48**: 992-998 [PMID: 16949492 DOI: 10.1016/j.jacc.2006.03.060]

49 **Monti LD**, Setola E, Fragasso G, Camisasca RP, Lucotti P, Galluccio E, Origgi A, Margonato A, Piatti P. Metabolic and endothelial effects of trimetazidine on forearm skeletal muscle in patients with type 2 diabetes and ischemic cardiomyopathy. *Am J Physiol Endocrinol Metab* 2006; **290**: E54-E59 [PMID: 16174656 DOI: 10.1152/ajpendo.00083.2005]

50 **Lee L**, Campbell R, Scheuermann-Freestone M, Taylor R, Gunaruwan P, Williams L, Ashrafian H, Horowitz J, Fraser AG, Clarke K, Frenneaux M. Metabolic modulation with perhexiline in chronic heart failure: a randomized, controlled trial of short-term use of a novel treatment. *Circulation* 2005; **112**: 3280-3288 [PMID: 16301359 DOI: 10.1161/CIRCULATIONAHA.105.551457]

51 **Morrow DA**, Scirica BM, Karwatowska-Prokopczuk E, Murphy SA, Budaj A, Varshavsky S, Wolff AA, Skene A, McCabe CH, Braunwald E. Effects of ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes: the MERLIN-TIMI 36 randomized trial. *JAMA* 2007; **297**: 1775-1783 [PMID: 17456819 DOI: 10.1001/jama.297.16.1775]

52 **Bern MM**. Platelet functions in diabetes mellitus. *Diabetes* 1978; **27**: 342-350 [PMID: 346421 DOI: 10.2337/diab.27.3.342]

53 **Dhule SS**, Gawali SR. Platelet aggregation and clotting time in type II diabetic males. *Natl J Physiol Pharm Pharmacol* 2014; **4**: 121-123 [DOI: 10.5455/njppp.2014.4.290920131]

54 **Güven F,** Yilmaz A, Aydin H, Korkmaz I. Platelet aggregation responses in type 2 diabetic patients. *Health* 2010; **2**: 708-712 [DOI: 10.4236/health.2010.27108]

55 **Sami S**, Willerson JT. Contemporary treatment of unstable angina and non-ST-segment-elevation myocardial infarction (part 2). *Tex Heart Inst J* 2010; **37**: 262-275 [PMID: 20548800]

56 **Hotta N**, Akanuma Y, Kawamori R, Matsuoka K, Oka Y, Shichiri M, Toyota T, Nakashima M, Yoshimura I, Sakamoto N, Shigeta Y. Long-term clinical effects of epalrestat, an aldose reductase inhibitor, on diabetic peripheral neuropathy: the 3-year, multicenter, comparative Aldose Reductase Inhibitor-Diabetes Complications Trial. *Diabetes Care* 2006; **29**: 1538-1544 [PMID: 16801576 DOI: 10.2337/dc05-2370]

57 **Bril V**, Hirose T, Tomioka S, Buchanan R. Ranirestat for the management of diabetic sensorimotor polyneuropathy. *Diabetes Care* 2009; **32**: 1256-1260 [PMID: 19366965 DOI: 10.2337/dc08-2110]

58 **Hotta N**, Toyota T, Matsuoka K, Shigeta Y, Kikkawa R, Kaneko T, Takahashi A, Sugimura K, Koike Y, Ishii J, Sakamoto N. Clinical efficacy of fidarestat, a novel aldose reductase inhibitor, for diabetic peripheral neuropathy: a 52-week multicenter placebo-controlled double-blind parallel group study. *Diabetes Care* 2001; **24**: 1776-1782 [PMID: 11574441 DOI: 10.2337/diacare.24.10.1776]

59 **Schemmel KE**, Padiyara RS, D'Souza JJ. Aldose reductase inhibitors in the treatment of diabetic peripheral neuropathy: a review. *J Diabetes Complications* 2010; **24**: 354-360 [PMID: 19748287 DOI: 10.1016/j.jdiacomp.2009.07.005]

60 **Pitocco D**, Tesauro M, Alessandro R, Ghirlanda G, Cardillo C. Oxidative stress in diabetes: implications for vascular and other complications. *Int J Mol Sci* 2013; **14**: 21525-21550 [PMID: 24177571 DOI: 10.3390/ijms141121525]

61 **Mahmood D**, Singh BK, Akhtar M. Diabetic neuropathy: therapies on the horizon. *J Pharm Pharmacol* 2009; **61**: 1137-1145 [PMID: 19703362 DOI: 10.1211/jpp.61.09.0002]

62 **Pop-Busui R**. Cardiac autonomic neuropathy in diabetes: a clinical perspective. *Diabetes Care* 2010; **33**: 434-441 [PMID: 20103559 DOI: 10.2337/dc09-1294]

63 **Carrasco E**, Werner P, Casper D. Prostaglandin receptor EP2 protects dopaminergic neurons against 6-OHDA-mediated low oxidative stress. *Neurosci Lett* 2008; **441**: 44-49 [PMID: 18597941 DOI: 10.1016/j.neulet.2008.05.111]

64 **Csányi G**, Miller FJ. Oxidative stress in cardiovascular disease. *Int J Mol Sci* 2014; **15**: 6002-6008 [PMID: 24722571 DOI: 10.3390/ijms15046002]

65 **Lieb DC**, Parson HK, Mamikunian G, Vinik AI. Cardiac autonomic imbalance in newly diagnosed and established diabetes is associated with markers of adipose tissue inflammation. *Exp Diabetes Res* 2012; **2012**: 878760 [PMID: 22110481 DOI: 10.1155/2012/878760]

66 **Said G**. Diabetic neuropathy. *Handb Clin Neurol* 2013; **115**: 579-589 [PMID: 23931803 DOI: 10.1016/B978-0-444-52902-2.00033-3]

67 **Ziegler D**, Low PA, Litchy WJ, Boulton AJ, Vinik AI, Freeman R, Samigullin R, Tritschler H, Munzel U, Maus J, Schütte K, Dyck PJ. Efficacy and safety of antioxidant treatment with α-lipoic acid over 4 years in diabetic polyneuropathy: the NATHAN 1 trial. *Diabetes Care* 2011; **34**: 2054-2060 [PMID: 21775755 DOI: 10.2337/dc11-0503]

68 **Ziegler D**, Schatz H, Conrad F, Gries FA, Ulrich H, Reichel G. Effects of treatment with the antioxidant alpha-lipoic acid on cardiac autonomic neuropathy in NIDDM patients. A 4-month randomized controlled multicenter trial (DEKAN Study). Deutsche Kardiale Autonome Neuropathie. *Diabetes Care* 1997; **20**: 369-373 [PMID: 9051389 DOI: 10.2337/diacare.20.3.369]

69 **Ibrahimpasic K**. Alpha lipoic acid and glycaemic control in diabetic neuropathies at type 2 diabetes treatment. *Med Arch* 2013; **67**: 7-9 [PMID: 23678828 DOI: 10.5455/medarh.2013.67.7-9]

70 **Adaikalakoteswari A**, Rabbani N, Waspadji S, Tjokroprawiro A, Kariadi SH, Adam JM, Thornalley PJ. Disturbance of B-vitamin status in people with type 2 diabetes in Indonesia--link to renal status, glycemic control and vascular inflammation. *Diabetes Res Clin Pract* 2012; **95**: 415-424 [PMID: 22133652 DOI: 10.1016/j.diabres.2011.10.042]

71 **Al-Attas OS**, Al-Daghri NM, Alfadda AA, Abd-Alrahman SH, Sabico S. Blood thiamine and its phosphate esters as measured by high-performance liquid chromatography: levels and associations in diabetes mellitus patients with varying degrees of microalbuminuria. *J Endocrinol Invest* 2012; **35**: 951-956 [PMID: 22107884 DOI: 10.3275/8126]

72 **González-Ortiz M**, Martínez-Abundis E, Robles-Cervantes JA, Ramírez-Ramírez V, Ramos-Zavala MG. Effect of thiamine administration on metabolic profile, cytokines and inflammatory markers in drug-naïve patients with type 2 diabetes. *Eur J Nutr* 2011; **50**: 145-149 [PMID: 20652275 DOI: 10.1007/s00394-010-0123-x]

73 **Kohda Y**, Shirakawa H, Yamane K, Otsuka K, Kono T, Terasaki F, Tanaka T. Prevention of incipient diabetic cardiomyopathy by high-dose thiamine. *J Toxicol Sci* 2008; **33**: 459-472 [PMID: 18827445 DOI: 10.2131/jts.33.459]

74 **Rabbani N**, Alam SS, Riaz S, Larkin JR, Akhtar MW, Shafi T, Thornalley PJ. High-dose thiamine therapy for patients with type 2 diabetes and microalbuminuria: a randomised, double-blind placebo-controlled pilot study. *Diabetologia* 2009; **52**: 208-212 [PMID: 19057893 DOI: 10.1007/s00125-008-1224-4]

75 **Thornalley PJ**, Babaei-Jadidi R, Al Ali H, Rabbani N, Antonysunil A, Larkin J, Ahmed A, Rayman G, Bodmer CW. High prevalence of low plasma thiamine concentration in diabetes linked to a marker of vascular disease. *Diabetologia* 2007; **50**: 2164-2170 [PMID: 17676306 DOI: 10.1007/s00125-007-0771-4]

76 **Wong CY**, Qiuwaxi J, Chen H, Li SW, Chan HT, Tam S, Shu XO, Lau CP, Kwong YL, Tse HF. Daily intake of thiamine correlates with the circulating level of endothelial progenitor cells and the endothelial function in patients with type II diabetes. *Mol Nutr Food Res* 2008; **52**: 1421-1427 [PMID: 18925614 DOI: 10.1002/mnfr.200800056]

77 **Alkhalaf A**, Klooster A, van Oeveren W, Achenbach U, Kleefstra N, Slingerland RJ, Mijnhout GS, Bilo HJ, Gans RO, Navis GJ, Bakker SJ. A double-blind, randomized, placebo-controlled clinical trial on benfotiamine treatment in patients with diabetic nephropathy. *Diabetes Care* 2010; **33**: 1598-1601 [PMID: 20413516 DOI: 10.2337/dc09-2241]

78 **Moss CJ**, Mathews ST. Thiamin status and supplementation in the management of diabetes mellitus and its vascular comorbidities. *Vitam Miner* 2013; **2**: 1-6 [DOI: 10.4172/vms.1000111]

79 **Haupt E**, Ledermann H, Köpcke W. Benfotiamine in the treatment of diabetic polyneuropathy--a three-week randomized, controlled pilot study (BEDIP study). *Int J Clin Pharmacol Ther* 2005; **43**: 71-77 [PMID: 15726875 DOI: 10.5414/CPP43071]

80 **Du X**, Edelstein D, Brownlee M. Oral benfotiamine plus alpha-lipoic acid normalises complication-causing pathways in type 1 diabetes. *Diabetologia* 2008; **51**: 1930-1932 [PMID: 18663426 DOI: 10.1007/s00125-008-1100-2]

81 **Power RA**, Hulver MW, Zhang JY, Dubois J, Marchand RM, Ilkayeva O, Muoio DM, Mynatt RL. Carnitine revisited: potential use as adjunctive treatment in diabetes. *Diabetologia* 2007; **50**: 824-832 [PMID: 17310372 DOI: 10.1007/s00125-007-0605-4]

82 **Solfrizzi V**, Capurso C, Colacicco AM, D'Introno A, Fontana C, Capurso SA, Torres F, Gadaleta AM, Koverech A, Capurso A, Panza F. Efficacy and tolerability of combined treatment with L-carnitine and simvastatin in lowering lipoprotein(a) serum levels in patients with type 2 diabetes mellitus. *Atherosclerosis* 2006; **188**: 455-461 [PMID: 16384561 DOI: 10.1016/j.atherosclerosis.2005.11.024]

83 **Bang HO**, Dyerberg J. The bleeding tendency in Greenland Eskimos. *Dan Med Bull* 1980; **27**: 202-205 [PMID: 7438807]

84 **Ebbesson SO**, Devereux RB, Cole S, Ebbesson LO, Fabsitz RR, Haack K, Harris WS, Howard WJ, Laston S, Lopez-Alvarenga JC, MacCluer JW, Okin PM, Tejero ME, Voruganti VS, Wenger CR, Howard BV, Comuzzie AG. Heart rate is associated with red blood cell fatty acid concentration: the Genetics of Coronary Artery Disease in Alaska Natives (GOCADAN) study. *Am Heart J* 2010; **159**: 1020-1025 [PMID: 20569715 DOI: 10.1016/j.ahj.2010.03.001]

85 **Cicero AF**, Derosa G, Di Gregori V, Bove M, Gaddi AV, Borghi C. Omega 3 polyunsaturated fatty acids supplementation and blood pressure levels in hypertriglyceridemic patients with untreated normal-high blood pressure and with or without metabolic syndrome: a retrospective study. *Clin Exp Hypertens* 2010; **32**: 137-144 [PMID: 20374188 DOI: 10.3109/10641960903254448]

86 **Dona M**, Fredman G, Schwab JM, Chiang N, Arita M, Goodarzi A, Cheng G, von Andrian UH, Serhan CN. Resolvin E1, an EPA-derived mediator in whole blood, selectively counterregulates leukocytes and platelets. *Blood* 2008; **112**: 848-855 [PMID: 18480426 DOI: 10.1182/blood-2007-11-122598]

87 **Davidson MH**, Stein EA, Bays HE, Maki KC, Doyle RT, Shalwitz RA, Ballantyne CM, Ginsberg HN. 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**: 1354-1367 [PMID: 17825687 DOI: 10.1016/j.clinthera.2007.07.018]

88 **Tavazzi L**, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008; **372**: 1223-1230 [PMID: 18757090 DOI: 10.1016/S0140-6736(08)61239-8]

89 **Harris WS**. Omega-3 fatty acids and cardiovascular disease: a case for omega-3 index as a new risk factor. *Pharmacol Res* 2007; **55**: 217-223 [PMID: 17324586 DOI: 10.1016/j.phrs.2007.01.013]

90 **Jeppesen C**, Schiller K, Schulze MB. Omega-3 and omega-6 fatty acids and type 2 diabetes. *Curr Diab Rep* 2013; **13**: 279-288 [PMID: 23325534 DOI: 10.1007/s11892-012-0362-8]

91 **Kandasamy N**, Joseph F, Goenka N. The role of omega-3 fatty acids in cardiovascular disease, hypertriglyceridaemia and diabetes mellitus. *Br J Diabet Vasc Dis* 2008; **8**: 121-128 [DOI: 10.1177/14746514080080030301]

92 **Rizza S**, Tesauro M, Cardillo C, Galli A, Iantorno M, Gigli F, Sbraccia P, Federici M, Quon MJ, Lauro D. Fish oil supplementation improves endothelial function in normoglycemic offspring of patients with type 2 diabetes. *Atherosclerosis* 2009; **206**: 569-574 [PMID: 19394939 DOI: 10.1016/j.atherosclerosis.2009.03.006]

93 **Wang C**, Harris WS, Chung M, Lichtenstein AH, Balk EM, Kupelnick B, Jordan HS, Lau J. n-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. *Am J Clin Nutr* 2006; **84**: 5-17 [PMID: 16825676]

94 **Bosch J**, Gerstein HC, Dagenais GR, Díaz R, Dyal L, Jung H, Maggiono AP, Probstfield J, Ramachandran A, Riddle MC, Rydén LE, Yusuf S. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *N Engl J Med* 2012; **367**: 309-318 [PMID: 22686415 DOI: 10.1056/NEJMoa1203859]

95 **Boulton AJ**, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, Malik RA, Maser RE, Sosenko JM, Ziegler D. Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care* 2005; **28**: 956-962 [PMID: 15793206 DOI: 10.2337/diacare.28.4.956]

96 TensioClinic TensioMed™ Arteriograph and TensioMed™ program. Available from: URL: http//www.arteriograph.nl/?act=download&fid=173

97 **Serhiyenko V**, Serhiyenko A, Serhiyenko L. Nicotinamide and alpha-lipoic acid in the treatment of cardiovascular autonomic neuropathy in type 2 diabetic patients. *Atherosclerosis Suppl* 2006; **7**: 568 [DOI: 10.1016/S1567-5688(06)81819-2]

98 **Serhiyenko V**, Oleksyk O, Serhiyenko A. Effects of the omega-3 polyunsaturated fatty acids in the treatment of cardiovascular autonomic neuropathy in type 2 diabetes mellitus patients. *Atherosclerosis Suppl* 2006; **7**: 450

99 **Serhiyenko V**, Urbanovich A, Serhiyenko A, Segin V, Serhiyenko L. Simvastatin and omega-polyunsaturated fatty acids in the treatment of cardiomyopathy in type 2 diabetes. mellitus patients. *Atherosclerosis Suppl* 2008; **9**: 203 [DOI: 10.1016/S1567-5688(08)70811-0]

100 **Serhiyenko VA**, Serhiyenko AA, Segin VB, Sandurska SY, Azmi A. Metabolic effects of simvastatin and omega-3 polyunsaturated fatty acids in type 2 diabetic patients with cardiovascular autonomic neuropathy. *Diabetes Metab* 2012; **38**: Spec No: 113–114 [DOI: 10.1016/S1262-3636(12)71606-3]

101 **Sergienko VA**, Segin VB, Samir A, Sergienko AA. [The effect of long-chain polyunsaturated higher ω-3 fatty acids, benfotiamine and α-lipoic acid on the lipid metabolism in patients with diabetes mellitus type 2 and cardiovascular autonomic neuropathy]. *Zh Nevrol Psikhiatr Im S S Korsakova* 2013; **113**: 54-58 [PMID: 24429949]

102 **Barter P**, Ginsberg HN. Effectiveness of combined statin plus omega-3 fatty acid therapy for mixed dyslipidemia. *Am J Cardiol* 2008; **102**: 1040-1045 [PMID: 18929706 DOI: 10.1016/j.amjcard.2008.05.056]

103 **Serhiyenko VA**, Serhiyenko AA, Mankovsky BN. Correlation between arterial wall stiffness, N-terminal prohormone of brain natriuretic peptide, functional and structural myocardial abnormalities in patients with type 2 diabetes mellitus and cardiac autonomic neuropathy. *Diabetes mellitus* 2013; **4**: 72-77 [DOI: 10.14341/DM2013472-77]

104 **Serhiyenko VA**, Serhiyenko AA, Segin V. 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. *Rom J Diab Nutr Metab Diseases* 2014; **21**: 97–101 [DOI 10.2478/rjdnmd-2014-0014]

105 **Freeman R**. Clinical practice. Neurogenic orthostatic hypotension. *N Engl J Med* 2008; **358**: 615-624 [PMID: 18256396 DOI: 10.1056/NEJMcp074189]

106 **Figueroa JJ**, Basford JR, Low PA. Preventing and treating orthostatic hypotension: As easy as A, B, C. *Cleve Clin J Med* 2010; **77**: 298-306 [PMID: 20439562 DOI: 10.3949/ccjm.77a.09118]

107 **Shin S**, Kim KJ, Chang HJ, Lee BW, Yang WI, Cha BS, Choi D. The effect of oral prostaglandin analogue on painful diabetic neuropathy: a double-blind, randomized, controlled trial. *Diabetes Obes Metab* 2013; **15**: 185-188 [PMID: 22974254 DOI: 10.1111/dom.12010]

108 **Tesfaye S**, Selvarajah D. Advances in the epidemiology, pathogenesis and management of diabetic peripheral neuropathy. *Diabetes Metab Res Rev* 2012; **28** Suppl 1: 8-14 [PMID: 22271716 DOI: 10.1002/dmrr.2239]

109 **Ziegler D**. [Can diabetic polyneuropathy be successfully treated?]. *MMW Fortschr Med* 2010; **152**: 64-68 [PMID: 20384102]

110[**Vinik AI**](http://www.ncbi.nlm.nih.gov/pubmed/?term=Vinik%20AI%5BAuthor%5D&cauthor=true&cauthor_uid=23550085)**,**[Erbas T](http://www.ncbi.nlm.nih.gov/pubmed/?term=Erbas%20T%5BAuthor%5D&cauthor=true&cauthor_uid=23550085), [Casellini CM](http://www.ncbi.nlm.nih.gov/pubmed/?term=Casellini%20CM%5BAuthor%5D&cauthor=true&cauthor_uid=23550085). Diabetic cardiac autonomic neuropathy, inflammation and cardiovascular disease. *J Diabetes Investig* 2013; **4**: 4-18 [PMID: 23550085 DOI: 10.1111/jdi.12042]

111 **Vinik AI**, Bril V, Kempler P, Litchy WJ, Tesfaye S, Price KL, Bastyr EJ. Treatment of symptomatic diabetic peripheral neuropathy with the protein kinase C beta-inhibitor ruboxistaurin mesylate during a 1-year, randomized, placebo-controlled, double-blind clinical trial. *Clin Ther* 2005; **27**: 1164-1180 [PMID: 16199243 DOI: 10.1016/j.clinthera.2005.08.001]

112 **Rhee SY**, Kim YS, Chon S, Oh S, Woo JT, Kim SW, Kim JW. Long-term effects of cilostazol on the prevention of macrovascular disease in patients with type 2 diabetes mellitus. *Diabetes Res Clin Pract* 2011; **91**: e11-e14 [PMID: 20934769 DOI: 10.1016/j.diabres.2010.09.009]

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**Table 1** **N-terminal fragment of the prohormone brain natriuretic peptide level and lipid metabolism parameters after 3-mo of omega-3 polyunsaturated fatty acid therapy**

|  |  |  |
| --- | --- | --- |
| **Parameter** | **Patients with T2DM and CAN (*n* = 36)** | |
| **Control (*n* = 15)** | **ω-3 PUFA (*n* = 21)** |
| **Group 1** | **Group 2** |
| NT-proBNP | -3.0 ± 1.1 | -6.8 ± 1.1a |
| LDL cholesterol | -8.3 ± 1.4 | -12.8 ± 1.9 |
| HDL cholesterol | +4.1 ± 1.0 | +7.1 ± 0.5a |
| ТG | -8.3 ± 1.2 | -35.4 ± 2.6c |
| TC | -6.7 ± 1.0 | -8.2 ± 1.1 |

The results are presented as % change from baseline, (Δ %, Mean ± SEM); a*P* < 0.05, b*P* < 0.01, c*P* < 0.001.T2DM: Type 2 Diabetes mellitus; CAN: Cardiac autonomic neuropathy; ω-3 PUFA: Omega-3 polyunsaturated fatty acid; NT-proBNP: N-terminal fragment of the prohormone brain natriuretic peptide; LDL cholesterol: Low density lipoprotein cholesterol; HDL cholesterol: High density lipoprotein cholesterol; ТG: Triglycerides; TC: Total cholesterol.

**Table 2 Сhanges of the immunoreactive insulin, leptin, high reactive C-reactive protein and tumor necrosis factol alpha levels after 3-mo of treatment**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter** | **Patients with T2DM and CAN (*n* = 81)** | | | | |
| **1st group (*n* = 15)** | **2nd group**  **(*n* = 21)** | **3rd group**  **(*n* = 12)** | **4th group**  **(*n* = 18)** | **5th group**  **(*n* = 15)** |
| IRI | -6.8 ± 2.0 | -10.3 ± 1.1 | -12.7 ± 1.4a | -15.9 ± 1.6b, e | -20.9 ± 0.9c, f, i, j |
| Leptin | -7.1 ± 1.8 | -15.8 ± 1.7b | -6.4 ± 1.4f | -16.3 ± 1.2c, i | -18.4 ± 1.4c, i |
| hsCRP | -7.2 ± 1.6 | -14.8 ± 2.4a | -13.3 ± 2.1a | -15.2 ± 1.9b | -22.6 ± 1.6c, e,h, k |
| TNF-α | -6.1 ± 1.0 | -14.1 ± 2.1b | -10.2 ± 1.6a | -14.7 ± 1.8 c | -19.8 ± 1.6c, d, i, l |

The results are presented as % change from baseline, (Δ %, Mean ± SEM); a*P* < 0.05, b*P* < 0.01, c*P* < 0.001 –compared to 1st group; d*P* < 0.05, e*P* < 0.01, f*P* < 0.001 –compared to 2nd group; g*P* < 0.05, h*P* < 0.01, i*P* < 0.001 –compared to 3rd group; j*P* < 0.05, k*P* < 0.01, l*P* < 0.001 –compared to 4th group. T2DM: Type 2 Diabetes mellitus; CAN: Cardiac autonomic neuropathy; IRI: immunoreactive insulin; hsCRP: High reactive C-reactive protein; TNF-α: Tumor necrosis factol alpha.

**Table 3 Сhanges of the lipid metabolism parameters after 3-mo of treatment**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter** | **Patients with T2DM and CAN (*n* = 81)** | | | | |
| **1st group (*n* = 15)** | **2nd group**  **(*n* = 21)** | **3rd group**  **(*n* = 12)** | **4th group**  **(*n* = 18)** | **5th group**  **(*n* = 15)** |
| LDL cholesterol | -8.3 ± 1.4 | -12.8 ± 1.9 | -7.6 ± 1.0d | -14.2 ± 1.8a, h | -33.1 ± 2.4c,f, i, l |
| HDL cholesterol | +4.1 ± 1.0 | +7.1 ± 0.5a | +5.7 ± 0.6 | +7.8 ± 0.7b, g | +13.9 ± 1.3c,f, i, l |
| ТG | -8.3 ± 1.2 | -35.4 ± 2.6c | -13.3 ± 3.4f | -9.3 ± 1.1f | -27.9 ± 3.9c, h, l |
| TC | -6.7 ± 1.0 | -8.2 ± 1.1 | -7.1 ± 1.2 | -10.7 ± 1.3a, g | -27.2 ± 1.9c,f, i, l |

The results are presented as % change from baseline, (Δ %, Mean ± SEM); a*P* < 0.05, b*P* < 0.01, c*P* < 0.001 –compared to 1st group; d*P* < 0.05, e*P* < 0.01, f*P* < 0.001–compared to 2nd group; g*P* < 0.05, h*P* < 0.01, i*P* < 0.001 –compared to 3rd group; j*P* < 0.05, k*P* < 0.01, l*P* < 0.001 –compared to 4th group. T2DM: Type 2 Diabetes mellitus; CAN: Cardiac autonomic neuropathy; LDL cholesterol: Low density lipoprotein cholesterol; HDL cholesterol: High density lipoprotein cholesterol; ТG: Triglycerides; TC: Total cholesterol.

**Table 4 Arterial stiffness parameters in patients with type 2 diabetes mellitus and cardiac autonomic neuropathy**

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **Control (*n* = 12)** | **Patients with T2DM without CVD and CAN (*n* = 12)** | **Patients with T2DM and CAN (*n* = 21)** |
| **1st group** | **2nd group** | **3rd group** |
| AIxao (%) | 20.6 ± 1.71 | 26.7 ± 1.84a | 33.7 ± 1.24c,e |
| AIxbr (%) | -33.7 ± 2.86 | -23.4 ± 1.91b | -7.9 ± 2.67c, f |
| PWV (m/s) | 7.2 ± 0.31 | 8.9 ± 0.25c | 11.1 ± 0.39c, f |
| AASI | 0.3 ± 0.02 | 0.36 ± 0.02a | 0.47 ± 0.03c, e |

Δ %, Mean ± SEM; a*P* < 0.05, b*P* < 0.01, c*P* < 0.001 –compared to 1st group; d*P* < 0.05, e*P* < 0.01, f*P* < 0.001 –compared to 2nd group. T2DM: Type 2 Diabetes mellitus; CAN: Cardiac autonomic neuropathy; CVD: Cardiovascular diseases; AIxao: Aortha augmentation index; AIxbr: Brachial augmentation index; PWV: Pulse wave velocity; AASI: Ambulatory arterial stiffness index.

**Table 5 Changes of day arterial stiffness parameters after 3 mo omega-3 polyunsaturated fatty acid therapy**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Patients with T2DM and CAN (*n* = 39)** | | | |
| **Groups** | **Baseline** | **After treatment** | **% change from baseline** |
| AIxao (%) | Control group | 30.4 ± 1.97 | 28.4 ± 1.68 | -4.3 ± 4.76% |
| Treatment group | 32.0 ± 1.32 | 26 4 ± 1.12b | -16.2 ± 3.12% |
| AIxbr (%) | Control group | -10.6 ± 3.37 | -12.0 ± 3.11 | -19.3 ± 12.14% |
| Treatment group | -9.8 ± 2.76 | -14.3 ± 2.84 | -42.8 ± 9.0% |
| PWV (m/s) | Control group | 10.2 ± 0.4 | 9.6 ± 0.4 | -6.0 ± 2.21% |
| Treatment group | 11.0 ± 0.35 | 9.7 ± 0.39a | -11.6 ± 2.09% |

The results are given as absolute values and as % change from baseline, (Δ %, Mean ± SEM); a*P* < 0.05, b*P* < 0.01, c*P* < 0.001 –compared to baseline. T2DM: Type 2 diabetes mellitus; CAN: Cardiac autonomic neuropathy; AIxao: Aortha augmentation index; AIxbr: Brachial augmentation index; PWV: Pulse wave velocity.

**Table 6 Changes of night arterial stiffness parameters after 3 mo omega-3 polyunsaturated fatty acid therapy**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Patients with T2DM and CAN (*n* = 39)** | | | |
| **Groups** | **Baseline** | **After treatment** | **% change from baseline** |
| AIxao (%) | Control group | 33.2 ± 1.98 | 30.1 ± 1.27 | -6.6 ± 4.15% |
| Treatment group | 36.6 ± 1.65 | 31.7 ± 1.23a | -11.2 ± 4.2% |
| AIxbr (%) | Control group | -4.2 ± 2.8 | -5.9 ± 2.48 | -10.0 ± 17.23% |
| Treatment group | -1.6 ± 2.79 | -10.4 ± 3.23a | -98.0 ± 18.1% |
| PWV (m/s) | Control group | 10.9 ± 0.4 | 10.3 ± 0.36 | -4.93 ± 1.41% |
| Treatment group | 11.3 ± 0.48 | 9.0 ± 0.44b | -18.9 ± 3.9% |

The results are given as absolute values and as % change from baseline, (Δ %, Mean ± SEM); a*P* < 0.05, b*P* < 0.01, c*P* < 0.001 –compared to baseline. T2DM: Type 2 diabetes mellitus; CAN: Cardiac autonomic neuropathy; AIxao: Aortha augmentation index; AIxbr: Brachial augmentation index; PWV: Pulse wave velocity.