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REVIEW

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

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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 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 B_1, 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 A_2 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

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 B_1 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. 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] 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 B_1, 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; Ca^{2+} 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 secretagogues: 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 ventricular (LV) hemodynamic parameters[27]. However, GLP-1 medication can not be used in pharmacological therapy of CVD as under influence of dipeptidyl peptidase-4 (DPP-4), GLP-1 is rapidly destroyed (effective half-life is only 1-2 min). Exenatide is 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 (sitagliptin). 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: Fibrates limit 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 LDL (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 colesevelam 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 HbA_{1c} 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 D_2[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 O_2 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 Ca^{2+} 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 Ca^{2+} 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. 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 O_2 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 Ca^{2+}-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 diabetic cardiomyopathy, 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, VO_2max 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 interval prolongation[51].

Limitation of extracellular Ca^{2+} into the cell: Blockers of Ca^{2+}-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 Ca^{2+} 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, Ca^{2+} 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 macro-elements, primarily Mg^{2+}: One of the risk factors that can decrease insulin sensitivity is hypomagnesaemia. It is suggested that Mg^{2+} 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].

ARI

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 advanced glycation endproducts, 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 by clinical 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 angiotensin-converting-enzyme 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 trandolapril for 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[4-6,11].

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 B_1 (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 reabsorption 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 B_1, or benfotiamine (monophosphate S-benzoyl-thiamine, high-bioavailable liposoluble vitamin B_1 derivatives). Results of experimental and clinical studies suggest a positive effect of benfotiamine prescription on prevention of diabetic vascular disease progression. Benfotiamine 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. Benfotiamine favoring the transketolase (TK) activity prevents the activation of pathophysiological mechanisms by reorientation towards of F6P and GAPDH metabolism[73-75]. Benfotiamine can promote neuronal and vascular deficiency correction through participation of nitrogen oxide processes, which have a significant therapeutic potential for the treatment of CVD. 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 benfotiamine and α-LA to patients with T1DM was followed by normalization of hyperglycemia and for 4 wk it promoted the normalization of prost-acyclin 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 pyruvate 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 glucose 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 cyclic endoperoxide synthase, including prostaglandin H_2, TXA_2 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, inhibits the proliferation of smooth muscle cells. However, the studies aimed to investigate the features of ω-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

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) Group 1	ω-3 PUFA (n = 21) Group 2
NT-proBNP	-3.0 ± 1.1	-6.8 ± 1.1[a]
LDL cholesterol	-8.3 ± 1.4	-12.8 ± 1.9
HDL cholesterol	4.1 ± 1.0	7.1 ± 0.5[a]
TG	-8.3 ± 1.2	-35.4 ± 2.6[c]
TC	-6.7 ± 1.0	-8.2 ± 1.1

The results are presented as % change from baseline, (Δ%, Mean ± SEM); [a]P < 0.05, [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; TG: Triglycerides; TC: Total cholesterol.

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[2,90-92].

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 HbA_{1c} 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 HbA_{1c} 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); leptin level-from Immunotech Leptin (Czech Republic) test kits; TNF-α-from Vector-Best (Russia); high-sensitivity C-reactive protein (hsCRP)-from diagnosis-related group (United States); N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP)-from Biomedica (Austria) kits and an enzyme-linked immunosorbent assay analysis technique. Lipid metabolism was assessed by the concentration of TC, LDL-, HDL-, VLDL-cholesterol measurements. The lipid fractions were determined by using HUMAN reagents (Germany) for the analyzer HUMANLAYZER 2000.

We found out that the HbA_{1c} 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. Changes of NT-proBNP and lipid metabolism parameters among patients with T2DM and CAN after 3-mo of ω-3 PUFA therapy are given in Table 1.

Benfotiamine 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 benfotiamine 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 level [7.8% ± 0.7%, (P < 0.01)]. Combined ω-3 PUFA, benfotiamine 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, aorta (AIxao) and brachial augmentation index (AIxbr), pulse wave velocity (PWV) and ambulatory arterial stiffness index (AASI) were

Table 2 Changes 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 ± 1.4^{a}	-15.9 ± 1.6^{b,e}	-20.9 ± 0.9^{c,f,i,j}
Leptin	-7.1 ± 1.8	-15.8 ± 1.7^{b}	-6.4 ± 1.4^{f}	-16.3 ± 1.2^{c,i}	-18.4 ± 1.4^{c,i}
hsCRP	-7.2 ± 1.6	-14.8 ± 2.4^{a}	-13.3 ± 2.1^{a}	-15.2 ± 1.9^{b}	-22.6 ± 1.6^{c,e,h,k}
TNF-α	-6.1 ± 1.0	-14.1 ± 2.1^{b}	-10.2 ± 1.6^{a}	-14.7 ± 1.8^{c}	-19.8 ± 1.6^{c,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; $^{h}P < 0.01$, $^{i}P < 0.001$ - 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 Changes 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 ± 1.0^{d}	-14.2 ± 1.8^{a,h}	-33.1 ± 2.4^{c,f,i,l}
HDL cholesterol	4.1 ± 1.0	7.1 ± 0.5^{a}	5.7 ± 0.6	7.8 ± 0.7^{b,g}	13.9 ± 1.3^{c,f,i,l}
TG	-8.3 ± 1.2	-35.4 ± 2.6^{c}	-13.3 ± 3.4^{f}	-9.3 ± 1.1^{f}	-27.9 ± 3.9^{c,h,l}
TC	-6.7 ± 1.0	-8.2 ± 1.1	-7.1 ± 1.2	-10.7 ± 1.3^{a,g}	-27.2 ± 1.9^{c,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; $^{d}P < 0.05$, $^{f}P < 0.001$ - compared to 2nd group; $^{g}P < 0.05$, $^{h}P < 0.01$, $^{i}P < 0.001$ - compared to 3rd group; $^{l}P < 0.001$ - 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; TG: Triglycerides; TC: Total cholesterol.

assessed by TensioMed™ 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 (Tables 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 approximately 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 electrocardiography, 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

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

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

Δ%, Mean ± SEM; [a]P < 0.05, [b]P < 0.01, [c]P < 0.001 - compared to 1st group; [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 ± 1.12[b]	-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 ± 0.39[a]	-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, - 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 ± 1.23[a]	-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 ± 3.23[a]	-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 ± 0.44[b]	-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, - compared to baseline. T2DM: Type 2 diabetes mellitus; CAN: Cardiac autonomic neuropathy; AIxao: Aortha augmentation index; AIxbr: Brachial augmentation index; PWV: Pulse wave velocity.

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 α_1-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), TXA_2 blockers and drugs that contribute into strengthening and/or normalization of Na^+, K^+-ATPase (cilostazol-a potential phosphodiesterase 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.

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