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Diabetic Cardiovascular Autonomic Neuropathy: Promising Therapeutic Perspective



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Abstract

Cardiac autonomic neuropathy (CAN) is a serious and common complication of type 2 diabetes mellitus (T2D). 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 T2D 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 hypocaloric diet and physical activity; optimization of glycemic control, first of all biguanides, treatment of dyslipoproteinemia, correction of metabolic abnormalities in myocardium, prevention and treatment of thrombosis, use of aldose reductase inhibitors, dihomogamma-linolenic acid (DGLA), acetyl-L carnitine, antioxidants, first of all alpha-lipoic acid (alpha-LA), use of omega-3 and omega-6 polyunsaturated fatty acids (omega-3 and omega-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), alpha-LA, DGLA, omega-3 PUFAs, and the simultaneous prescription of alpha-LA, omega-3 PUFA and DGLA.

Keywords: Type 2 diabetes mellitus; Cardiac autonomic neuropathy; Treatment

Abbreviations: CAN: Cardiac Autonomic Neuropathy; T2D: Type 2 Diabetes Mellitus; DGLA: Dihomo-gamma-Linolenic Acid; alpha-LA: A-Lipoic Acid; omega-3 and omega-6 PUFAs: Omega-3 and Omega-6 Poly Unsaturated Fatty Acids; DM: Diabetes Mellitus; CVD: Cardio Vascular Diseases; GLP-1: Glucagon-Like Peptide-1; DLP: Dys Lipo Proteinemia; ARI: Aldose Reductase Inhibitors; OS: Oxidative Stress; EPA: Eicosa Pentaenoic Acid; DHA: Docosa Hexaenoic Acid; DBP: Diastolic Blood Pressure

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 (T2D)] are diagnosed with cardiovascular diseases (CVD) due to coronary vessels arterial sclerotic disease. Often the course of CVD 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]. CAN among T2D 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" myocardial infarction, sudden death syndrome [3-5]. The aim of this study is to review the latest evidence about the treatment perspectives of patients with T2D and CAN.

Problem of effective treatment of CAN is particularly relevant. Pathogenetic treatment of CAN includes: balanced diet and physical activity; optimization of glycemic control, first of all biguanides; treatment of dyslipoproteinemia; correction of metabolic abnormalities in myocardium; prevention and treatment of thrombosis; use of aldose reductase inhibitors, gamma-linolenic acid, acetyl-L-carnitine, dihomogamma-linolenic acid (DGLA), antioxidants, first of all alpha-lipoic acid (alpha-LA), use of omega-3 and omega-6 polyunsaturated fatty acids(omega-3 and omega-6 PUFAs), vasodilators, fat-soluble vitamin B₁, aminoguanidine;

substitutive therapy of growth factors and others [4,6]. It is obvious that the foreground should be therapy aimed at reducing insulin resistance, correction of hyperglycemia, prevention and treatment of cardiomyopathy, symptomatic treatment of concomitant diseases and syndromes (hypertension, CVD, heart failure and arrhythmias) [4]. In this regard it is necessary to perform the following preventive and remedial therapy.

Discussion

Lifestyle modification, Nutrition and physical activity, Correction of obesity. Limit salt intake to 2-4g/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. Physical activity is associated with higher heart rate variability and lower heart rate, therefore may be a predictor of positive changes in heart rate variability indices [7].

Compensation state of T2D is recognized as a primary goal in the prevention of development and/or progression of CVD [8,9]. Insulin resistance (IR) is a defining feature in most cases of T2D 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 [10].

Insulin and/or insulin secretagogues

Theoretically, their use may improve glucose metabolism in the myocardium and reduce the content of circulating free fatty acids, however, the assignment of these pharmacological agents is not conducive to the prevention of CVD in the experiment [4].

Glucagon-Like Peptide-1 (GLP-1) medication

The experiment established that the use of GLP-1 improves the functional state of left ventricular hemodynamic parameters [4]. However, GLP-1 medication cannot be used in pharmacological therapy of CVD as under influence of dipeptidyl peptidase-4, GLP-1 is rapidly destroyed (effective half-life is only 1-2 min).

Treatment of dyslipoproteinemia (DLP)

For DLP pharmacotherapy using statins, fibrates, bile acid sequestrants, nicotinic acid and its derivatives, products of ω -3 and ω -6 polyunsaturated fatty acids (ω -3 and ω -6 PUFAs), or as an alternative-their combination with cholesterol absorption inhibitors [11-13].

Modulators of metabolism

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. Perhexiline prescription to patients with heart failure significantly contributes to the improvement of ejection fraction, VO_2 max and quality of life. Unfortunately, the clinical

use of this medicament is limited because of the risk of hepatotoxicity and peripheral neuropathy. Ranolazine is the third antianginal pharmacological agent with a potential of metabolism modifier. However, the following factors do not allow implementing 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 [4].

Limitation of extracellular Ca^{2+} into the cell

Prescription of β -adrenergic receptor blockers for T2D with CVD and CAN has significant pathogenetic grounds as high sympathetic activity that is followed by CAN, accelerates the development of CVD and significantly affects prognosis. 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. Cardioselective β -blockers can also balance the effects of autonomic dysfunction in particular by resisting sympathetic stimulation they can restore parasympathetic-sympathetic balance [14,4].

Aldose reductase inhibitors (ARI) inhibit the glucose polyol way metabolism; prevent the reduction of the redox potentials. Zoporestat, ranirestat-medicaments of a new generation of ARI group showed sufficient efficacy in experimental studies [6,4]. Aminoguanidine improves capacity of nerve velocity, increases blood flow, inhibits the formation of advanced glycation endproducts, and delays the emergence and development of albuminuria. The use of aminoguanidine derivatives is accompanied by clinical efficacy and lack of adverse side effects [4]. 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 [15,16]. Vitamins with antioxidant properties [a liposoluble vitamin B_1 (benfotiamin)], combined medications. There are enough experimental and clinical results of studies that suggest that the hyperinsulinemia, IR, and chronic hyperglycemia in T2D have a negative impact on the metabolism of thiamine. 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 B1 derivatives) [4].

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. 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 T2D 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 [4]. 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 T2D and DLP) [4,17,18]. In addition, ω -3 PUFA moderately reduce blood pressure, improve endothelial function, reduce proinflammatory status and improve antioxidant protection.

Conclusion

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), thromboxane A₂ 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. In addition, the combination of α -LA, ω -3 PUFAs, DGLA and ARI is the most rational path genetically justified use.

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