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Relationship Between Cardiac Autonomic Neuropathy and Atherosclerosis in Patients with Diabetes Mellitus

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Abstract

Cardiovascular disease is the major cause of death in diabetic patients. Diabetes mellitus patients have a 4-fold-higher risk of having a cardiovascular event than people without diabetes. Cardiac autonomic neuropathy is a frequent and severe complication of diabetes mellitus. Definite cardiac autonomic neuropathy is present in one fifth of diabetic patients. Cardiac autonomic neuropathy diagnosis is associated with a 5-fold increase in mortality, higher prevalence of silent myocardial ischemia as well as systolic and diastolic left ventricular dysfunction. In the last several years many works described a significant relationship between cardiac autonomic neuropathy and atherosclerotic vascular disease in type 1 and type 2 diabetes mellitus population. Our review focuses on possible pathophysiological pathways binding these two important diabetic complications.

Keywords: Autonomic neuropathy; Diabetes mellitus; Atherosclerosis; Arterial stiffness

Introduction

Patients with type 1 and type 2 diabetes mellitus have significantly higher risk of cardiovascular disease including coronary artery disease(CAD), stroke, and peripheral arterial disease comparing to non-diabetic population [1-3]. Cardiovascular disease is the major cause of death in diabetic patients (approximately 70%) [4,5]. Type 2 diabetes mellitus patients have a 4-fold-higher risk of having a cardiovascular event than people without diabetes after adjusting to common risk factors of atherosclerosis, such as age, tobacco smoking, obesity, hyperlipidemia and hypertension. Major cardiovascular event (such as myocardial infarction, coronary revascularization, stroke, acute coronary heart disease death) is 3 times more often in type 1 diabetic men and up to 7 times more often in type 1 diabetic women [5,6].

Prolonged hyperglycemia is considered to be a main cause of diabetic microvascular and macrovascular complications [4,7,8]. Chronic hyperglycemia induces the production of advanced glycation end products (AGEs) through the non-enzymatic glycation process, alters intracellular signaling cascades (protein kinase C activation), and increases oxidative stress. All these mechanisms interact and lead to many structural and functional changes of the vascular wall inducing the atherosclerosis development [9]. Hyperglycemia also increases platelet aggregation, risk of thrombus formation and atherosclerosis progression [10].

In patients with type 2 diabetes mellitus, obesity and fatty tissue accumulation lead to lipid metabolism changes and pro-inflammatory markers production. In these subjects, insulin resistance is critically involved in vascular dysfunction [11,12]. Cardiac autonomic neuropathy (CAN) is a frequent and severe complication of diabetes mellitus. Definite CAN is present in one fifth of diabetic patients [13]. CAN diagnosis is associated with a 5-fold increase in mortality comparing to diabetic patients without CAN, and a higher prevalence of silent myocardial ischemia as well as systolic and diastolic left ventricular dysfunction [14-16]. CAN incidence correlates to QT prolongation and increase the risk of malignant arrhythmias and sudden cardiac death [17]. In the last several years many works described a significant relationship between cardiac autonomic neuropathy and atherosclerotic vascular disease in type 1 and type 2 diabetes mellitus population [18-24].

Are cardiac autonomic neuropathy together with accelerated atherosclerosis only products of prolonged unsatisfactory metabolic compensation or is there a pathophysiological mechanism

that promotes atherosclerosis development in patients suffering CAN? We would like to address these questions in our review.

Risk factors of CAN and atherosclerosis

Age, diabetes mellitus, high cholesterol and low density lipoprotein levels, low level of high density lipoprotein, hypertension, tobacco smoke, obesity and inactive lifestyle are now considered to be major risk factors of atherosclerosis [25].

Some of these factors were also found to be risk markers of CAN. A meta-analysis of Dafaalla et al. from 2016 found that age, duration of diabetes, glycated hemoglobin level, BMI, serum triglycerides, hypertension and incidence of microvascular complications are directly related to the risk of CAN development in type 1 diabetes mellitus [26]. Similar findings applies for CAN in type 2 diabetes mellitus. Reduced heart rate variability(an indicator of CAN) in type 2 diabetes mellitus patients is also in association with obesity and smoking [16]. Poor glycemic control seems to be a major risk for CAN progression in diabetic patient [27-29]. Many risk factors of atherosclerosis and diabetic CAN overlap, especially in type 2 diabetes mellitus patients. But what is the exact mechanism of CAN development? Is it only a result of vasa nervorum ischemia or do also other pathogenic pathways take a part?

Pathogenesis of CAN

Pathogenesis of CAN is complex, multifactorial and not entirely clear. Multiple ethiological hypotheses were proposed including hyperglycemia induced nerve fibers injury, autoimmune damage and neurohormonal growth factor deficiency [15,29,30].

Hyperglycemia

Long term hyperglycemia is considered to be a leading cause of micro and macrovascular complications of diabetes mellitus. Hyperglycemia leads through the alteration of many metabolic pathways to endothelial dysfunction, decreased neuronal blood flow and nerve fiber damage. Excess of glucose activates the polyol pathway leading to sorbitol accumulation. NADPH is consumed as a coenzyme in this process. Relative deficiency of NADPH may cause impaired NO synthesis and decreased nerve blood flow [15,31]. Hyperglycemia induced metabolic changes result in increased free radicals production and oxidative stress that lead to vascular endothelium damage [15]. Accelerated advanced glycation end (AGE) products formation alters the membrane permeability as well as neuronal and endothelial function [32]. Increased formation of diacylglycerol lead to the subsequent activation of protein kinase C(PKC). PKC pathway affects the regulation of endothelial permeability, vasoconstriction, extracellular matrix synthesis, abnormal angiogenesis and cytokine activation [33]. All these mechanisms result in functional and structural changes of vessels (including vasa nervorum) and nerve fibers.

Autoimmunity

The role of autoimmunity on diabetic autonomic neuropathy is also discussed. Several studies proved the independent association of nervous tissue antibodies and CAN presence in patients with T1DM [15,29,34-36]. One of the most recent prospective study with adolescent T1DM patients was published in 2014. Zanone et al. has followed 66 patients for 16 years. 19 of them had circulating autobodies(Ab) to autonomic tissues. Prevalence of abnormal cardiovascular autonomic tests and autonomic symptoms were higher in Ab-positive (68 and 26%) than Ab-negative (32 and 4%) patients ($P < 0.05$) independent of glycemic control [37]. Study of Shigeta et al. found that the presence of circulating sulfatide and phospholipid antibodies correlates with diabetic neuropathy in 68 T2DM patients [38,39]. However more studies are needed to prove the role of autoimmunity on diabetic autonomic neuropathy in T2DM patients.

Genetic predisposition

Many genes were found to have an association with the development or progression of diabetic neuropathy (i.e. ACE, MTHFR, GST, GLO1, APOE, TCF7L2, VEGF, IL-4, GPX1, eNOS, ADRA2B, GFRA2, MIR146A, MIR128A) [40]. Some of the studies were focused to find gene polymorphisms correlation with diabetic autonomic neuropathy. Genes associated with autonomic dysfunction code for example an antioxidant enzyme (Glutathione S-transferase), transcription factor (TCF7L2 gene) or autonomic nervous sysem receptor (alpha2B-adrenergic receptor) [40-42].

Possible pathogenic pathways binding CAN and atherosclerosis progression

It seems that autonomic neuropathy is not only a microvascular complication, but several pathophysiological mechanisms are involved in its development. Let's have a look from the other side. How could CAN contribute to atherosclerosis development and progression?

Non-dipping and Hypertension

The autonomic nervous system is responsible for the optimal regulation of the heart rate, strength of cardiac muscle contraction and vessel tone. The renin-angiotensin-aldosterone system controls the body fluid volume. Both of these systems interact and regulate the blood pressure. Blood pressure, along with the heart rate, physiologically decreases during the sleep period as a result of the higher tone of the parasympathetic nervous system. This phenomenon is called nocturnal dipping and it is at least 10% drop of blood pressure in comparison to average daily values. It is known that nerve fiber loss is length-dependent. That explains predominant parasympathetic (vagus nerve) impairment in early stages of CAN [31]. Vagal nerve dysfunction and relative hyperactivity of the sympathetic nervous system in early stages of CAN is the most probable cause of insufficient drop of blood pressure during the sleep (so called blood pressure „nondipping „) or even rise of blood pressure during the night (so called „reverse dipping") [27,43,44].

Nondipping and reverse dipping is associated with left ventricular hypertrophy and cardiovascular events [45-48]. A meta-analysis of Cuspidi et al. proved the association between nondipping and increased risk of subclinical atherosclerosis [49]. Moreover a prospective study which monitored 75 adolescent

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T1DM patients found that the abnormal blood pressure pattern during the night period also precedes the development of microalbuminuria (marker of glomerular and vascular dysfunction) [50]. All these studies support a statement of Vinik and his colleagues from 2003 who suggested that an impaired circadian pattern of sympathovagal activity with higher blood pressure values during the night and subsequent complications could represent an important link between CAN and an increased risk of mortality in diabetic patients [15].

Arterial stiffness

Thera are also data indicating that CAN is associated with arterial stiffness [51-53]. Arterial stiffness leads to higher arterial wall resistance and increases systolic blood pressure. Higher systolic blood pressure promotes atherosclerosis development. Again we are confronted with the question whether CAN and arterial stiffness are common results of chronic bad diabetic compensation or whether they interact. As we discussed above, early stages of CAN are accompanied by prevalent parasympathetic impairment leading to relative hyperactivity of sympathetic nervous system. Higher sympathetic tone leads to tachycardia in rest. In rat animal models, an artificial increase of heart rate determines the reduction of arterial distensibility [54-56]. Moreover, vagal denervation is associated with higher procollagen mRNA levels in the wall of affected vessels [57]. Sympathetic denervation may cause dedifferentiation of vascular smooth muscle cells and intima thickening [58]. These findings suggest that the autonomic nervous system alterations have a negative trophic effect on arterial wall and could lead to increased arterial stiffness. This hypothesis seems to be supported by a prospective study of Prince et al. published in 2010. It showed that CAN (expressed as decreased heart rate variability in deep breathing test) is associated with increased arterial stiffness 18 years later in type 1 diabetes mellitus patients [59].

Inflammatory pathway

Experimental studies showed that the autonomic nervous system modulates the systemic inflammatory response through the cholinergic anti-inflammatory pathway [60,61]. Rodrigues et al. [19] who published in 2010 an interesting study that proved that reduced heart rate variability(marker of CAN) predicts the progression of coronary artery calcification in adults with and without T1DM, suggested that autonomic neuropathy leading to pro-inflammatory state could represent one pathway leading to atherosclerosis progression [19]. A study from 2017 found an association of lower heart rate variability(HRV) and white blood cells count(WBCC), this study also described an inverse association of inflammatory markers(WBCC and CRP) with baroreflex sensitivity and carotid plaque area [62]. Another study described an association of lower HRV parameters, presence of depression and higher IMT with CRP and IL6 [63]. Nevertheless more studies are needed to confirm how could autonomic dysfunction activate the inflammatory system and promote atherosclerosis.

All mentioned pathophysiological pathways binding CAN and atherosclerosis are summarized on simplified schema (Figure 1).

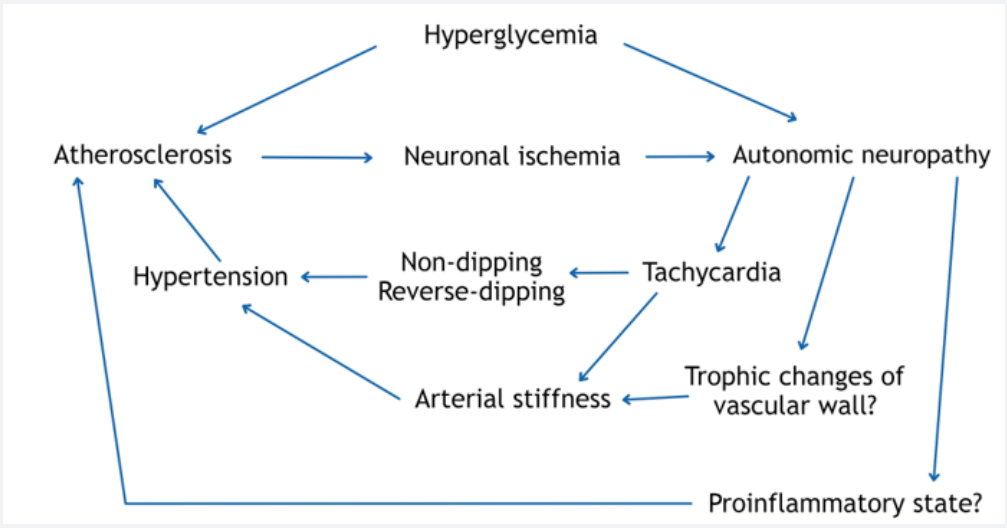

Figure 1: Discussed pathophysiological pathways binding CAN and atherosclerosis.

Discussion

Our review focused on the relationship between CAN and atherosclerosis development in diabetic patients. Although some risk factors of atherosclerosis overlap with the risk factors of CAN, it seems that the pathophysiology of CAN is more complex and multifactorial. Several small studies found a significant correlation between the presence of circulating autonomic tissue autobodies and diabetic autonomic neuropathy. The role of genetic polymorphisms and epigenetic changes of several genes associated with autonomic function is also discussed.

It seems that both of these diabetic complications interact and mutually affect the progression of each other. We discussed the possible pathways (heart rate and blood pressure increase, trophic changes of arterial wall, arterial stiffness, pro-inflammatory state) through which CAN may contribute to atherosclerosis progression. Future prospective studies on young diabetic patients with

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good glycemic control and free of macrovascular complications could help to identify the exact pathophysiological mechanisms between these two units and hopefully find a way how to decrease cardiovascular mortality in diabetic patients.

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