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Diabetic Autonomic Neuropathies as Complications of Insulin and Non-insulin Dependent Diabetes Mellitus

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Abstract—*Changes in human behaviour and lifestyle over the last century have resulted in a dramatic increase in the incidence of diabetes worldwide. Diabetic autonomic neuropathies are a heterogeneous and progressive disease entity which is commonly seen to complicate both type 1 and type 2 diabetes mellitus. Although the etiology is unclear, lack of insulin, hyperglycemia, autoimmune mimicking mechanisms and metabolic abnormalities are thought to play a pivotal role. A subgroup of diabetic autonomic neuropathy (DAN), cardiovascular autonomic neuropathy (CAN), which is one of the classical complications of diabetes mellitus (DM), but yet, one of the least frequently diagnosed, is ultimately important because of its correlation with increased mortality. The natural history of CAN is not well understood, but is thought to develop from a subclinical stage characterized by an impaired baroreflex sensitivity and abnormalities of spectral analysis of heart rate variability... The pathogenesis of CAN is complex and involves a cascade of pathways activated by hyperglycemia eventually resulting in progressive neuronal ischemia and cellular death. Early diagnosis of CAN, using scintigraphic imaging techniques or spectral analysis of heart rate variability might pave way for screening of patients at highest risk for the development of CAN and, thereby, enable the targeting of intensive therapeutic approaches. No form of therapy in DAN has been identified that provides unequivocal, safe, and effective stabilization or reversal of the condition The aim of this article is to review the epidemiology, potential causes and consequences, diagnosis and promising therapeutic approaches of diabetic autonomic neuropathy*

1. 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 ofCHD 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. 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. The aim of this study is to review the latest evidence and own data about the treatment perspectives of patients with DM and CAN.

2. THE EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF DIABETIC NEUROPATHY

Diabetic peripheral neuropathy (DPN) is a common complication estimated to affect 30–50% of individuals with diabetes[3].The primary risk factor for DPN is hyperglycaemia [3,4] Other independent risk factors include age, duration of disease, cigarette smoking, hypertension, elevated triglycerides, higher BMI, alcohol consumption, and taller height [3,4]. Interestingly, between 25 and 62% of patients with idiopathic peripheral neuropathy are reported to have prediabetes; among these 11–25% are thought to have peripheral neuropathy, and 13–21% have neuropathic pain [5]. Population-based studies suggest a gradient for the prevalence of neuropathy, being highest in patients with manifest diabetes

mellitus, followed by individuals with impaired glucose tolerance, then by subjects with impaired fasting glucose and, finally, least in those with normo-glycaemia [5]. It is generally believed that oxidative stress is the key pathological process inducing nerve damage in diabetes.Oxidative stress, possibly triggered by vascular abnormalities and associated microangiopathy in the nerve, is a key pathological process inducing nerve damage in diabetes in humans and experimental models. Diabetes-induced oxidative stress in animal models of type 1, type 2 and pre-diabetes in sensory neurons and peripheral nerves is demonstrated by increased production of reactive oxygen species, lipid peroxidation and protein nitrosylation, and diminished levels of reduced glutathione and ascorbate. Treatment with antioxidants such as α-lipoic acid, γ-linolenic acid and aldose reductase inhibitors prevent many indices of neuropathy in streptozotocin-diabetic rats. Sensing ongoing spontaneous pain and paroxysmal shooting pain in the absence of any external stimulus is caused by ectopic impulse generation within the nociceptive pathways [6]. The enhanced excitability can result from altered ion channel function such as an increase in persistent sodium currents. Persistent sodium currents can be reliably estimated using threshold tracking. In peripheral neuropathy, persistent sodium currents usually increase, possibly due to over-expression of sodium channels associated with axonal regeneration, and could be responsible for ectopic firings. In diabetic neuropathy, the activation of the polyol pathway mediated by an enzyme, aldose reductase, leads to reduced Na + /K + pump activity and intra-axonal sodium accumulation; sodium currents are reduced presumably due to decreased transaxonal sodium gradient. In addition to voltage-gated sodium channels, several other ion channels probably undergo alterations after a nerve lesion, such as voltage-gated potassium channels, which might also contribute to changes in membrane excitability of nociceptive nerves[6]. Further potent inhibitory neurons, such as descending pathways originating in the brainstem, contribute to modulation of pain processing. Lesions that affect these opiodergic and monoaminergic systems also lead to pain exacerbation via disinhibition [6].

3. FORMS OF DIABETIC NEUROPATHY

Several fairly distinct clinical syndromes of diabetic neuropathy have been delineated. The most common, as noted, is a distal, symmetrical, primarily sensory polyneuropathy affecting feet and legs in a chronic, slowly progressive manner.

3.1 Sensorimotor Neuropathy

Distal Sensory Diabetic Polyneuropathy This is the most common presentation of neuropathy in diabetes, and up to 50% of patients may experience symptoms–most frequently burning pain, electrical or stabbing sensations, paraesthesia, hyperaesthesia, and deep aching pain [7].

3.2 Acute Diabetic Mononeuropathies

Cranial neuropathy in diabetic patients most commonly involves the oculomotor nerve followed by the trochlear and facial nerve in order of frequency. Thirdnerve palsy with pupillary sparing is the hallmark of diabetic oculomotor palsy and is attributed to nerve infarction [8]

3.3 Diabetic Multiple Mononeuropathies and Radiculopathies

This category overlaps with the mononeuropathies. A syndrome of painful unilateral or asymmetrical multiple neuropathies tends to occur in older patients with relatively mild or even unrecognized diabetes.

Autonomic Neuropathy Diabetic autonomic neuropathy is a widespread disorder of the cholinergic, adrenergic and peptidergic autonomic fibres in the context of diabetes without other causes. It is characterized by a subclinical form that is detectable only by tests, and a clinical form with the presence of signs and symptoms [9]

3.4 Cardiovascular Autonomic Neuropathy

CAN is defined as the impairment of autonomic control of the cardiovascular system. In diabetes, CAN is ultimately the result of complex interactions among degree of glycaemic control, disease duration, age-related neuronal attrition and systolic and diastolic blood pressure [9].

3.5 Gastrointestinal Autonomic Neuropathy

Gastrointestinal motor, sensory and secretory functions are modulated by the interaction of the autonomic (sympathetic and parasympathetic) and enteric nervous systems with underlying rhythmicity generated by the interstitial cells of Cajal located within the smooth muscle. Evaluation of gastrointestinal autonomic function is difficult in humans, and the diagnosis of gastrointestinal autonomic neuropathy is often one of exclusion [9].

3.6 Diabetic Sudomotor Dysfunction

Diabetic autonomic neuropathy initially results in a loss of thermoregulatory sweating in a ‘glove and stocking’ distribution that can extend to the upper parts of the limbs and the anterior abdomen, conforming to the well recognised length dependency of diabetic neuropathy.

4. PATHOGENESIS OF CAN

The exact pathogenesis of CAN is complex and remains unclear. Most of the proposed mechanisms of neuronal injury are based on models of somatic rather than autonomic neuropathy.

4.1 Hyperglycaemia induced neuronal injury and ischaemia

The pathogenesis of CAN is likely to be multi-factorial 10 and to involve several mechanisms and pathways that lead to

neuronal ischaemia or direct neuronal death/dysfunction. Hyperglycaemia and the adverse metabolic environment in patients with DM result in increased oxidative and nitrosative stress which can cause direct neuronal damage/dysfunction as well as endothelial dysfunction resulting in neuronal ischaemia. Neuronal axons are rich in mitochondria which makes them particularly susceptible to the direct and indirect effects on oxidative and nitrosative stress.

4.2 Autoimmunity

The role of autoimmunity has also been explored particularly in patients with T1DM. The presence of complement-fixing antibodies against sympathetic and para-sympathetic tissues in patients with insulin-dependent diabetes and their correlation with CAN was described in the early 90s.

4.3 Residual β -cell function

Several studies have shown a protective effect of residual β-cell function (*i.e.,* C-peptide levels) on the development and incidence of microvascular complications (including CAN) in patients with T1DM. The exact mechanisms for these associations are not clear but it is thought that the C-peptide activates Na/K channels, lowers inflammation and improves NO bioavailability and endothelial function. Small RCTs have shown beneficial effect of C-peptide treatment on CAN parameters.

Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) is emerging as another possible factor in the development of CAN. OSA is very common in patients with diabetes and has been associated with increased sympathetic tone in patients without diabetes [11]. The interrelationship between OSA and CAN in patients with DM requires further investigation and is likely to be bidirectional. Furthermore, the presence of CAN was associated with more severe apnoea/hypopnea episodes

5. NATURAL HISTORY OF CAN

DM affects the autonomic (as well as the peripheral) nervous system in an ascending length-dependent manner. The vagus nerve, which anatomically is the longest autonomic nerve and physiologically mediates 75% of the overall parasympathetic activity, tends to be involved early in the course of CAN development. The early stages of CAN therefore involve reduction in parasympathetic activity, which results in sympathetic predominance. This increase in sympathetic tone continues until the latest stage of CAN when sympathetic denervation ensues, which spreads gradually from the apex to the base of the heart. CAN is divided into a sub-clinical and a clinical stage. During the initial sub-clinical stage, CAN is detected through abnormalities in frequency and time domains of the spectral analysis of HRV and the Baroreflex Sensitivity (BRS) tests, as well as an increased torsion of the left ventricle (LV) on cardiac imaging before the development of abnormalities in standard cardiac autonomic reflex testing (CART) [12] Studies have shown that these abnormalities can even be present at the time of diagnosis of DM[12]. CAN progresses and parasympathetic denervation is followed by compensatory sympathetic overdrive, resulting in abnormal CARTs followed by symptomatic CAN in which the clinical manifestations become apparent At the stage of sympathetic denervation, autonomic dysfunction correlates clinically with postural hypotension[12]. The time scale for the progression of subclinical CAN to the development of abnormal CART is unclear; similarly the natural history of the development of early cardiac abnormalities (such as torsion or deficits in myocardial perfusion or cardiac energetic) and its relationship to subclinical CAN is also unclear. But we estimate that many patients with sub-clinical CAN will develop abnormal CART and early features of cardiac involvement within 5 years of developing abnormal frequency and time domain parameters.

6. CLINICAL MANIFESTATIONS OF CAN

6.1 Resting tachycardia

Resting tachycardia is a common manifestation of CAN that occurs at a relatively early stage of the disease. A HR of 90-130 beats per minute (bpm) can be observed and is associated with a reduction in parasympathetic tone followed by increased sympathetic activity as CAN progresses[13]. A fixed HR which does not change during sleep, exercise or stress is a sign of complete cardiac denervation. Moreover, poor HR response to adenosine is associated with higher risk for adverse cardiac events, including all-cause and CVD mortality. Hence, resting HR can be used as a diagnostic and prognostic tool in patients with DM after excluding other causes of tachycardia.

6.2 Exercise intolerance

Impaired blood pressure, HR and cardiac stroke volume in response to exercise in the absence of structural or coronary cardiac disease are all features of CAN. As disease progresses, the parasympathetic-sympathetic imbalance can lead to further impairment of the above parameters [13] which limits the diagnostic utility of exercise tolerance testing in these patients due to increased false negative outcomes caused by blunted HR response. In addition, patients with CAN should be tested using stress cardiac imaging (usually echocardiography) prior to starting an exercise program, especially those with high-risk profile.

6.3 Orthostatic hypotension

Orthostatic hypotension is a manifestation of advanced CAN. Orthostatic hypotension is defined as the reduction in systolic blood pressure by > 20 mmHg or in diastolic blood pressure by > 10 mmHg 2 min following postural change from supine to standing. Orthostatic hypotension occurs as a result of the impairment of the sympathetic response to postural change secondary to poor norepinephrine response and abnormalities in the baro-receptor sensitivity, resulting in inadequate HR

response and peripheral vasoconstriction. Orthostatic hypotension can be aggravated by many medications that are commonly used in patients with DM such as diuretics, vasodilators, tricyclic antidepressants and insulin. Similar to resting tachycardia, assessing the presence of orthostatic hypotension is of prognostic value as a marker of advanced CAN. In the middle-aged general population, orthostatic hypotension has been shown to be an independent prognostic factor for CVD and all cause mortality[14].

6.4 Silent ischaemia

CAN is associated with a prolonged subjective angina threshold (which is defined as the time between the observation of 1 mm ST depression on the electrocardiogram and the development of symptoms of angina pectoris); thus rendering patients with CAN susceptible for experiencing silent myocardial ischaemia and potentially infarction, despite being asymptomatic.

6.5 Diabetic cardiomyopathy and LV dysfunction

Diabetic cardiomyopathy is a clinical entity that is characterized by changes in the biochemical signalling in the presence of a sympathetic-vagal imbalance resulting ultimately in left ventricular hypertrophy and remodelling, and therefore cardiac dysfunction in patients with DM in the absence of coronary artery disease. Diabetic cardiomyopathy results in variable degrees of systolic and predominantly diastolic dysfunction in the absence of structural or valvular cardiac disease, coronary vessel disease, or hypertension. Changes in the diastolic and/or systolic function can be identified on various diagnostic imaging modalities in otherwise asymptomatic patients and can precede the occurrence of macrovascular diabetic complications. Frequently, the only detectable abnormality in the early stages of CAN is an isolated diastolic dysfunction with a normal LV ejection fraction associated with high CVD morbidity.

6.6 Mortality/sudden death

CAN is associated with an increased mortality risk. This was described in longitudinal studies in the early 1990s showing a 50% increase in 5 year-mortality risk in patients with DM and autonomic neuropathy compared to those without [15].

6.5 Perioperative and intraoperative complications

Patients with CAN exhibit 2- to 3-times fold increase in perioperative morbidity (perioperative complications, impaired wound healing, impaired drug metabolism) and mortality. Patients with CAN are more likely to require vasopressor support in the theatre setting. They are also prone to experience a blood pressure and HR reduction during the induction of anaesthesia, as well as severe intraoperative hypothermia.The above findings can be explained by an impairment or absence of the normal vasoconstrictive response to vasodilating anaesthesia in patients with CAN.

6.6 Diabetic nephropathy

Several authors have hypothesized that CAN is involved in the pathogenesis of diabetic nephropathy, although causation has not been proven Sympathetic overactivity has been shown to cause glomerular and tubular dysfunction in diabetic animal models *via* indirect (hypertension and angiotensin-II) and direct (vascular smooth muscles proliferation, vasoconstriction, podocytes injury) insults.

7. CARDIOVASCULAR CONSEQUENCES

Impaired heart rate variability HRV is a physiological variation in the interval between heartbeats and is regulated by the interaction of the sympathetic and parasympathetic tone. The functional response to the instantaneous metabolic needs of the body is regulated by this beat-to-beat variation. As high variability reflects the cardiac ability to adapt and implies good health, damage or disturbances to this control system results in lower HRV values. Even in a normal heart rate, the first finding of CAN is a decrease in HRV, which is apparent at the subclinical stage and can be detected through deep respiration.

7.1 Resting tachycardia

Due to the dominant sympathetic tone, resting heart rates of 90 to 100 beats per minute with occasional increases to as many as 130 beats per minute are frequent findings in CAN with vagal impairment[16]. Highest resting heart rates have been shown in patients with lone parasympathetic impairment[16]. As the disease progresses and involves both parasympathetic and sympathetic nerves, the heart rate tends to return to the normal range but remains higher than in healthy individuals[16].It is showed that resting heart rate is independently associated with CAN and has a high predictive value in predicting CAN in the general population. A steady heart rate less responsive to exercise, stress or sleep is suggestive of almost total cardiac denervation, which indicates severe CAN.

7.2 Exercise intolerance

Exercise tolerance is worsened by CAN through the blunting of the increases in heart rate, blood pressure and cardiac output response to exertion. The development of hypotension or hypertension following strenuous exercise is more likely in individuals with CAN, particularly in the onset of a new exercise program. Therefore, patients with diabetes probably to have CAN should be checked for cardiac stress before beginning to exercise. Due to poor thermoregulation, such patients should avoid exercising in environments that are too hot or cold and hydrate adequately.

7.3 Silent myocardial ischemia

Coronary artery disease has long been considered as a major complication of diabetes mellitus. Numerous studies have reported more extensive atherosclerotic disease, particularly

that of the coronary arteries, in diabetic individuals. Silent myocardial ischemia is defined as the objective documentation of myocardial ischemia without angina or its equivalents.

7.4 Sudden death

CAN is associated with a higher risk of malignant arrhythmias and sudden death. Previous studies have found 5-year mortality rates between 16% and 50% in patients with both CAN and either type of diabetes, often attributed to sudden cardiac death. Severe asymptomatic ischemia inducing fatal arrhythmias has been reported as the leading potential cause.

7.5 Stroke

Previous studies have revealed the relationship between CAN and cerebrovascular events. It is reported that the presence of CAN, assessed by HRV testing, was significantly associated with the ischemic stroke in a study of 1458 patients with type 2 diabetes with a 7-year follow-up. Another study of 133 subjects with type 2 diabetes showed that stroke could be predicted by parasympathetic and sympathetic autonomic function abnormalities.

8. DIAGNOSTIC METHODS OF CARDIAC AUTONOMIC NEUROPATHY

Variability in heart rate and blood pressure values can provide data regarding both parasympathetic and sympathetic autonomic function and is useful in clinical settings.

8.1 Heart rate variability

The most commonly used methods for the diagnosis of CAN are based on HRV assessment. HRV testing is noninvasive and objective in the evaluation of cardiac autonomic function and can be performed by recording electrocardiograms during deep breathing, standing, and Valsalva maneuvers[17]. HRV analysis enables the independent measurement of the sympathetic and parasympathetic components of the autonomic nervous system and can be assessed with a number of simple clinical tests] or easier digital 24-h electrocardiographic recordings[18].

8.2 Time domain methods

Time domain methods determine the heart rate at any point in time or the intervals between consecutive normal complexes[18]. Each QRS complex is detected and the normal-to-normal (NN) intervals (that is all intervals between adjacent QRS complexes resulting from sinus node depolarizations) or the instantaneous heart rate is determined through a continuous ECG record.

Frequency domain methods

CAN may also be evaluated using spectral analysis of HRV, which divides the R-R signal into sine and cosine waves to estimate the amount of variability as a function of frequency[18].

8.3 Heart rate turbulence

Another Holter-based technique for evaluating CA is the heart rate turbulence (HRT)[19]. HRT refers to sinus rhythm cycle length fluctuations following isolated premature ventricular beats. After an initial acceleration, the sinus rate decelerates after a premature ventricular beat. There are 2 components of HRT; turbulence onset and turbulence slope.

Other diagnostic tools

Other methods currently used in research settings are scintigraphic evaluation of sympathetic innervation of the heart, which can reveal cardiac sympathetic nerve population changes and early anatomical regional deficits of sympathetic denervation; microneurography, which records electrical activity released by peroneal, tibial or radial sympathetic nerves and identifies sympathetic dysfunction; neurovascular flow, using noninvasive laser Doppler measures of peripheral sympathetic reactions to nociception; and baroreflex sensitivity, which evaluates the capability to reflexively increase vagal activity in response to a sudden increase in blood pressure.. As many of these tests assess the influence on sympathetic component, they do not provide information about early stage CAN. In a recent study, it was shown that altered cardiac autonomic balance can be detected through exercise stress testing in diabetic subjects even with minimal evidence of CAN[20].

9. THERAPEUTIC APPROACHES

Early determination of CAN is significant for the success of therapeutic strategies as cardiovascular denervation seems to be reversible at onset[21]. In less affected patients, lifestyle changes including graded supervised exercise associated with weight loss improve HRV[21].

9.1 Optimizing glycemic control

Blood glucose optimization is the essential treatment for CAN. The Framingham Heart Study showed the significant association between reduced HRV and increased fasting plasma glucose level[22]. This finding is present in diabetics as well as individuals with impaired glucose tolerance.

9.2 Preventive Treatment

Based on the aetiology of diabetic neuropathy several agents have been tested to halt its progression thereby improving clinical out-come [23]. An analysis of the literature on experimental peripheral diabetic neuropathy suggests that, to date, all of the pharmacological agents shown to counteract one or several manifestations of painful or insensate neuropathy also have efficacy against nerve conduction velocity deficit [23].

9.3 Symptomatic Treatment–Painful Diabetic Neuropathy

Tricyclic Antidepressants. Tricyclic antidepressants (TCAs) are so-called early antidepressant medications. These first-generation medications were effective in the treatment of depression because they enhanced serotonergic or noradrenergic mechanisms or both. They were also the first medication category that proved effective for neuropathic pain in placebo-controlled trials [24].

Selective Serotonin Reuptake Inhibitors. The SSRI are increasingly being used to treat a spectrum of depressed patients, including the elderly. As a class, SSRIs have comparable efficacy to TCAs against depression but are generally better tolerated [25]. Despite their wide use there is still limited evidence for the role of classical SSRIs in the treatment of painful diabetic neuropathy .

Other Agents. Local lidocaine and capsaicin cream have been shown to be effective in the treatment of neuropathic conditions [26]. They are included as potential therapeutic options in the recent AAN guidelines [27].Acupuncture, bu not traditional Chinese herbal medicine, seems to be slightly effective [28]. Transcutaneous electric nerve stimulation should also be considered in the treatment of painful diabetic neuropathy .

10. CONCLUSION

Sensorimotor and cardiovascular neuropathies are common in diabetic patients. Apart from strict glycaemic control, no further therapeutic approach exists in the prevention of this phenomenon. The reasons that only some patients with nerve lesions develop neuropathic pain are still unknown. Risk factors such as age, gender, pain intensity before and after the lesion, and emotional and cognitive features indicate that there are multiple factors other than the nerve lesion itself that contribute to the manifestation of chronic pain. Diagnosis and symptomatic treatment are essential for these patients as painful sensorimotor neuropathies are associated with poor quality of life and autonomic neuropathies are associated with increased cardiovascular mortality. Intensive diabetes therapy, intensive multifactorial cardiovascular risk reduction and lifestyle intervention are recommended in patients with CAN. Although very common and serious, CAN is a frequently overlooked complication of diabetes. Related with intraoperative and perioperative cardiovascular instability, abnormal blood pressure profile, orthostatic hypotension cardiomyopathy, and stroke, CAN is associated with significant increases in morbidity and mortality. Patients may have subclinical CAN for several years before it becomes clinically apparent. Because the progression of cardiovascular denervation is partly reversible or can be slowed down in the early stages of the disease, recent guidelines strongly recommend screening for CAN in patients with diabetes. Orthostatic hypotension, which may lead to life-threatening injuries, is an undesired manifestation and indicates severe or advanced CAN.

REFERENCES

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

[2] American Diabetes Association. Standards of medical care in diabetes--2014. *Diabetes Care* 2014; **37** Suppl 1: S14-S80 [PMID: 24357209 DOI: 10.2337/dc14-S014].

[3] Deshpande AD, Harris-Hayes M, Schootman M: Epidemiology of diabetes and diabetes-related complications. Phys Ther 2008; 88: 1254–1264.

[4] Edwards JL, Vincent AM, Cheng HT, Feldman EL: Diabetic neuropathy: mechanisms to management. Pharmacol Ther 2008; 120: 1– 34.

[5] Papanas N, Vinik AI, Ziegler D: Neuropathy in prediabetes: does the clock start ticking early? Nat Rev Endocrinol 2011; 7: 682–690.

[6] Baron R, Binder A, Wasner G: Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol 2010; 9: 807–819.

[7] Boulton AJ, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, Malik RA, Maser RE, Sosenko JM, Ziegler D; American Diabetes Association Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care 2005; 28: 956–962.

[8] Bansal V, Kalita J, Misra UK: Diabetic neuropathy. Postgrad Med J 2006; 82: 95–100.

[9] Spallone V, Bellavere F, Scionti L, Maule S, Quadri R, Bax G, Melga P, Viviani GL, Esposito K, Morganti R, Cortelli P; Diabetic Neuropathy Study Group of the Italian Society of Diabetology: Recommendations for the use of cardiovascular tests in diagnosing diabetic autonomic neuropathy. Nutr Metab Cardiovasc Dis 2011; 21: 69–78.

[10] 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]

[11] Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. Lancet 2009; 373: 82-93 [PMID: 19101028 DOI: 10.1016/S0140-6736(08)61622-0]

[12] Kuehl M, Stevens MJ. Cardiovascular autonomic neuropathies as complications of diabetes mellitus. *Nat Rev Endocrinology* 2012; **8**: 405-416 [PMID: 22371159 DOI: 10.1038/nrendo. 2012.21]

[13] Pop-Busui R. What do we know and we do not know about cardiovascular autonomic neuropathy in diabetes. *J Cardiovasc Transl Res* 2012; **5**: 463-478 [PMID: 22644723 DOI: 10.1007/s12265-012-9367-6]

[14] Fedorowski A, Stavenow L, Hedblad B, Berglund G, Nilsson PM, Melander O. Orthostatic hypotension predicts all-cause mortality and coronary events in middle-aged individuals (The Malmo Preventive Project). *Eur Heart J* 2010; **31**: 85-91 [PMID: 19696189 DOI: 10.1093/eurheartj/ehp329]

[15] Pop-Busui R, Cleary PA, Braffett BH, Martin CL, Herman WH, Low PA, Lima JA, Bluemke DA. Association between cardiovascular autonomic neuropathy and left ventricular dysfunction: DCCT/EDIC study (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications). *J Am Coll Cardiol* 2013; **61**: 447-454 [PMID: 23265339 DOI: 10.1016/j.jacc.2012.10.028]

[16] Pop-Busui R. What do we know and we do not know about cardiovascular autonomic neuropathy in diabetes. *J Cardiovasc Transl Res* 2012; **5**: 463-478 [PMID: 22644723 DOI: 10.1007/s12265-012-9367-6]

[17] Ewing DJ, Campbell IW, Clarke BF. Assessment of cardiovascular effects in diabetic autonomic neuropathy and prognostic implications. *Ann Intern Med* 1980; **92**: 308-311 [PMID: 7356219 DOI: 10.7326/0003-4819-92-2-308]

[18] Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 1996; **93**: 1043-1065 [PMID: 8598068 DOI: 10.1161/01.CIR.93.5.1043]

[19] Bauer A, Malik M, Schmidt G, Barthel P, Bonnemeier H, Cygankiewicz I, Guzik P, Lombardi F, Müller A, Oto A, Schneider R, Watanabe M, Wichterle D, Zareba W. Heart rate turbulence: standards of measurement, physiological interpretation, and clinical use: International Society for Holter and Noninvasive Electrophysiology Consensus. *J Am Coll Cardiol* 2008; **52**: 1353-1365 [PMID: 18940523 DOI: 10.1016/j.jacc.2008.07.041].

[20] Banthia S, Bergner DW, Chicos AB, Ng J, Pelchovitz DJ, Subacius H, Kadish AH, Goldberger JJ. Detection of cardiovascular autonomic neuropathy using exercise testing in patients with type 2 diabetes mellitus. *J Diabetes Complications* 2013; **27**: 64-69 [PMID: 23083925 DOI: 10.1016/j.jdiacomp.2012.09.002]

[21] Howorka K, Pumprla J, Haber P, Koller-Strametz J, Mondrzyk J, Schabmann A. Effects of physical training on heart rate variability in diabetic patients with various degrees of cardiovascular autonomic neuropathy. *Cardiovasc Res* 1997; **34**: 206-214 [PMID: 9217892 DOI: 10.1016/ S0008-6363(97)00040-0].

[22] Singh JP, Larson MG, O'Donnell CJ, Wilson PF, Tsuji H, Lloyd-Jones DM, Levy D. Association of hyperglycemia with reduced heart rate variability (The Framingham Heart Study). *Am J Cardiol* 2000; **86**: 309-312 [PMID: 10922439 DOI: 10.1016/S0002-9149(00)00920-6]

[23] Obrosova IG: Diabetic painful and insensate neuropathy: pathogenesis and potential treatments. Neurotherapeutics 2009; 6: 638–647.

[24] Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, Bushnell MC, Farrar JT, Galer BS, Haythornthwaite JA, Hewitt DJ, Loeser JD, Max MB, Saltarelli M, Schmader KE, Stein C, Thompson D, Turk DC, Wallace MS, Watkins LR, Weinstein SM: Advances in neuropathic pain diagnosis, mechanisms, and treatment recommendations. Arch Neurol 2003; 60: 1524–1534.

[25] Jiang W, Davidson JR: Antidepressant therapy in patients with ischemic heart disease. Am Heart J 2005; 150: 871–881.\

[26] Smith HS, Argoff CE: Pharmacological treatment of diabetic neuropathic pain. Drugs 2011; 71: 557–589.

[27] Bril V, England J, Franklin GM, Backonja M, Cohen J, Del Toro D, Feldman E, Iverson DJ, Perkins B, Russell JW, Zochodne D: Evidence- based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology 2011; 76: 1758–1765.

[28] Chen W, Zhang Y, Liu JP: Chinese herbal medicine for diabetic peripheral neuropathy. Cochrane Database Syst Rev 2011; 6:CD007796.