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Disorders of circadian rhythms of heart rate variability in diabetic cardiac autonomic neuropathy: mechanisms and consequences

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Abstract. *Abnormalities in heart rate variability (HRV) may increase the risk of cardiovascular disease over the next six years from 4 to 10 %. It is reported that the probability of stroke or cardiac death can be immediately reduced by chronobiologically assessing HRV and optimizing timed treatment efficacy. Physiological cardiovascular activities are under the control of the cardiac autonomic nervous system. Damage to the autonomic nerves results in dysfunction in heart rate control and vascular dynamics, particularly in cardiac autonomic neuropathy (CAN). Autonomic imbalance in the sympathetic (SNS) and parasympathetic nervous systems (PSNS) regulation of cardiovascular function contributes to metabolic abnormalities and significant morbidity and mortality for individuals with diabetes mellitus (DM). Misalignment of circadian rhythms has been evidenced in patients with DM, and there is a close relationship between alterations in neuroendocrine sleep architecture, circadian clock oscillations, glucose metabolism, autonomic function, and diurnal profiles of blood pressure and heart rate. Metabolic syndrome, hypertension, myocardial infarction, and DM are characterized by increased SNS activity and decreased PSNS activity. However, type 2 DM patients had a decrease in both PSNS and SNS activity. It can be explained by type 2 DM, which is a metabolic disease responsible for CAN that affects both sympathetic and parasympathetic fibers. The purpose of this review was to discuss the current state of the problem of the relationship between DM and circadian rhythm disorders, HRV. Particular attention is paid to the risk factors of diabetic CAN; insights into the mechanisms of excess mortality associated with CAN; the pathogenesis of diabetic CAN; possible pathogenic pathways binding CAN and atherosclerosis progression; genetic and epigenetic factors and CAN; DM and circadian rhythms of HRV; diabetic CAN and circadian rhythm disorders. The search was conducted in Scopus, Science Direct (from Elsevier), and PubMed, including MEDLINE databases. The keywords used were diabetes mellitus, cardiac autonomic neuropathy, circadian rhythms, heart rate variability. A manual search of the bibliography of publications was used to identify study results that could not be found during the online search.*

Keywords: *diabetes mellitus; cardiac autonomic neuropathy; circadian rhythms; heart rate variability; review*

Introduction

A circadian rhythm is an oscillation of a physiological process over a 24-h period. Many cardiovascular (CV) variables, including heart rate (HR), heart rate variability (HRV), ECG waveforms, and blood pressure (BP), demonstrate a robust circadian rhythm [1]. Strictly speaking, an oscillation is considered circadian only if it persists over 24 h of darkness. Despite the lack of testing for cardiovascular variables in many cases, we describe the oscillations as circadian due to the widespread usage of this term [2]. Many cardiovascular diseases (CVDs) vary in prevalence according to the time of day, including myocardial infarction (MI), supraventricular/ventricular arrhythmias, and sudden cardiac death [3, 4].

Circadian clocks, which drive day-night oscillations with a free-running period of approximately 24 hours, control circadian rhythms. Others have extensively characterized and reviewed the molecular machinery of the circadian clock [5]. At its core is a negative feedback loop made up of four basic helix-loop-helix transcription factors, also known as per-arnt-sim domain transcription factors. These are CLOCK,

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BMAL1, PER, and CRY3. In the nucleus, CLOCK and BMAL1 work together as a heterodimer to bind to canonical enhancer or E-box regions in the promoters of the Per, Cry, and Rev-erb genes. This starts the transcription of these genes [6]. So, PER and CRY proteins slowly build up in the cytoplasm. Then, they join forces to go back into the nucleus and stop CLOCK/BMAL1 from starting the transcription of the Per and Cry genes. At the same time, the accumulation of REV-ERB suppresses the transcription of Clock and Bmal1. Together, this establishes a negative feedback loop. This full cycle takes about 24 hours [4, 5].

Most mammalian cells contain circadian clocks. External cues such as light synchronize the central circadian clock in the suprachiasmatic nucleus in the hypothalamus with the environment. Then, neurohumoral factors (such as autonomic tone, body temperature, and glucocorticoid signaling) bring clocks in peripheral tissues into sync with the central clock [7]. The intact heart exhibits oscillations in the expression of core circadian clock genes, and these oscillations persist in isolated cultured myocardial tissue and cardiomyocytes [5]. The heart's local clock controls up to 10 % of the cardiac transcriptome. As a result, key processes in the heart (including electrical excitability, signal transduction, and metabolism) vary in a circadian manner [3, 4].

Continuous 24-h ECG recordings from healthy volunteers have shown a circadian rhythm in the ECG. The RR interval increases at night, corresponding to a slowing of the HR. This nocturnal bradycardia seems to be independent of the nocturnal fall in BP. At night, there is also a lengthening of the PQ interval, QRS duration, and both uncorrected and corrected QT intervals [8]. This indicates slower atrioventricular node conduction, His-Purkinje conduction, and ventricular repolarization, respectively. Rodents display a similar circadian rhythm in their ECGs. Therefore, we understand the normal electrical properties of the sinus node, atrioventricular node, and the His-circadian release of other neurohumoral factors, but the impact on the circadian rhythm in HR remains unclear. Studies of day-night variations in HRV, a widely used indirect measure of cardiac autonomic tone, appear to support the role of autonomic tone [9].

But, studying the biophysics of HRV has shown that there is an exponential relationship between HRV and HR. This means that changes in HRV seen in people and rodents are mostly caused by changes in HR [10]. Interestingly, direct recordings of stellate ganglion nerve activity and vagal nerve activity in an ambulatory dog model of heart failure show a circadian rhythm in the sympathetic but not vagal tone of the heart [11]. These studies suggest that circadian sympathovagal balance may be largely due to diurnal fluctuations in sympathetic tone. Catecholamine secretion from the adrenal medulla also exhibits a prominent circadian rhythm; this may contribute to the circadian rhythm in HR [4, 12]. An alternative way to test the involvement of the autonomic nervous system (ANS) is to block autonomic control of the heart. The autonomic tone is the dominant mechanism by which the suprachiasmatic nucleus drives circadian changes in HR [3]. In their 2019 study, N. Black et al. suggest that the ANS affects the circadian rhythm in HR by keeping the local cardiac clock in sync to cause gene expression to change during the day [3].

Risk factors of diabetic cardiac autonomic neuropathy

Major risk factors of atherosclerosis include age, diabetes mellitus (DM), high total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels, low levels of high-density lipoprotein cholesterol (HDL-C), arterial hypertension (AH), tobacco smoke, obesity, and an inactive lifestyle [13]. Researchers also discovered that some of these factors serve as risk markers for cardiac autonomic neuropathy (CAN). M. Dafaalla et al. (2016) conducted a meta-analysis which revealed a direct relationship between the risk of CAN development in type 1 DM (T1DM) and factors such as age, duration of diabetes, glycated hemoglobin A1c level (HbA1c), body mass index (BMI), serum triglycerides, AH, and incidence of microvascular complications [14]. Similar findings apply for CAN in type 2 DM (T2DM) [15]. Reduced HRV (an indicator of CAN) in T2DM patients is also associated with obesity and smoking. Poor glycemic control seems to be a major risk for CAN progression in the diabetic patient [16, 17]. Many risk factors of atherosclerosis and diabetes CAN overlap, especially in T2DM patients. Nevertheless, what is the exact mechanism of CAN development? Is it only a result of vasa nervorum ischemia, or do other pathogenic pathways also take part [18, 19]?

Numerous prospective cohort studies have confirmed the identification of hyperglycemia, hyperlipidemia, and AH as the primary controllable risk factors for the progression of diabetic CAN [20, 21]. Previous studies also found that microvascular complications are the main risk factors for the diabetic CAN process [4, 22]. Numerous factors contribute to autonomic dysfunction in pre-diabetes and metabolic syndrome (MetS), manifesting as parasympathetic depression and sympathetic overactivity or predominance. There is evidence that when someone is insulin-resistant, their sympathetic nervous system is overactive. This is because insulin causes the sympathetic nervous system to activate through peripheral and central mechanisms, as well as upregulating chemoreflex. Obstructive sleep apnea (OSA) is often linked to being overweight or having T2DM. It also raises the chemoreflex, which leads to sympathetic hyperactivity [23, 24]. In addition to OSA, other factors in MetS may also cause autonomic dysfunction, potentially with a bidirectional relationship [25, 26], and subsequently exacerbate metabolic derangements at various levels [27, 28].

Insights into the mechanisms of excess mortality associated with CAN

The mechanisms of this CAN-associated excess mortality and morbidity remain mostly unknown. Several cardiovascular abnormalities have been found in association with CAN. They can represent: 1) a form of morbidity in themselves, such as silent myocardial ischemia; 2) a recognized risk factor or marker for mortality or morbidity (resting tachycardia, postural hypotension, QT interval prolongation, impairment of baroreflex sensitivity (BRS), nondipping, reduced HRV); 3) a potential pathogenetic links between CAN and mortality, such as an imbalance in sympathovagal activity, cardiac sympathetic dysinnervation, reduction in the sympathetically mediated vasodilatation of coronary vessels, dysregulation of cerebral circulation, new mechanisms like increased arterial

stiffness and coronary calcium content, or inflammation [28, 29]. Finally, peripheral vascular function abnormalities may exert a contributory role to diabetic foot complications. Some of these abnormalities are established risk markers for mortality and morbidity in diabetes [28, 29].

Pathogenesis of diabetic CAN

The exact cause of diabetic CAN is complicated and not fully understood. Several molecular processes are at play, such as high blood sugar, oxidative stress (OS), inflammation, and endothelial dysfunction (ED) [20, 30]. These mechanisms interact with each other, of which hyperglycemia is the major pathological factor [28, 31]. Chronic hyperglycemia, a result of worsening insulin resistance (IR), is a well-established characteristic of T2DM [28]. Furthermore, the increased expression of several inflammatory factors, including tumor necrosis factor-α and interleukin-6, is closely associated with IR [32]. Inflammatory cytokines also disrupt insulin signaling, thereby contributing to IR [32]. Therefore, IR can be involved in the diabetic CAN process via multiple mechanisms. Y. Liu et al. (2021) showed that in addition to IR reflected by fasting C-peptide, a computer version definitions of the Homeostasis Model Assessment of IR (HOMA-IR) and C-peptide index, two recognized factors independently associated with diabetic CAN; namely age and duration of diabetes, which is consistent with other studies [32]. Along with IR shown by fasting C-peptide, HOMA-IR and fasting C-peptide point to two known factors that are independently linked to diabetic CAN: age and time having diabetes, which is in line with previous research [28]. It was surprising, though, that HOMA-IR wasn't significantly linked to diabetic CAN. Instead, it was found that as HOMA-IR went up, so did diabetic CAN. This could be because the sample size was too small to find a statistically significant link with diabetic CAN after insulin-treated patients were taken out. This could be because the sample size was too small to find a statistically significant link with diabetic CAN after insulin-treated patients were taken out [33]. Cohort studies have confirmed the identification of hyperglycemia, hyperlipidemia, and AH as the primary controllable risk factors for the progression of diabetic CAN [32]. Y. Liu et al. (2021) showed that the LDL level increased significantly with the progression of diabetic CAN. Diabetic CAN showed a correlation with systolic blood pressure (SBP). However, the study did not observe a correlation between diabetic CAN and serum glucose. The present study, being a cross-sectional study that monitored serum glucose at a specific time, may have failed to reflect long-term fluctuations in serum glucose [32]. Previous studies also found that microvascular complications are the main risk factors for the diabetic CAN process [20]. The relationship between diabetic chronic The present study found a relationship between diabetic chronic kidney disease and the progression of diabetic CAN, as well as a correlation between indicators reflecting kidney function such as estimated glomerular filtration rate, urinary albumin excretion rate, and urine albumin-to-creatinine ratio association between diabetic CAN and diabetic peripheral neuropathy or diabetic retinopathy. These different conclusions might relate to the various study populations, diagnostic criteria, and different research methods; for instance, patients with proliferative diabetic retinopathy were not involved in the present study [32]. In addition to IR reflected by fasting C-peptide, HOMA-IR, and fasting C-peptide point to two recognized factors that are independently associated with diabetic CAN: age and diabetic duration, which is consistent with previous studies [28]. However, it was unexpected that HOMA-IR was not significantly correlated to diabetic CAN but was found to rise with increasing HOMA-IR, possibly due to the sample size after excluding the insulin-treated patients was too small to detect a statistically significant association with diabetic CAN [33].

Possible pathogenic pathways binding CAN and atherosclerosis progression

The relationship between CAN and atherosclerosis is well known [18, 34]. The ANS regulates HR and vascular tone, and its dysfunction may contribute to the development of atherosclerosis and arterial stiffness in patients with diabetes [35]. The SEARCH Cardiovascular Disease study suggested that even young patients with T1DM may present with signs of early autonomic dysfunction. Similarly, these subjects have shown a relationship between CAN and arterial stiffness, independent of other classic cardiovascular risk factors [36, 37]. However, we have not elucidated whether the presence of CAN is associated with concomitant asymptomatic peripheral artery disease (aPAD) in patients diagnosed with arterial stiffness. A study by L. Nattero-Chávez et al. (2019) suggested that CAN might be linked to both peripheral arterial stiffness (defined by an ankle-brachial index (ABI) > 1.2) and the presence of aPAD at the same time [38]. L. Nattero-Chávez et al. (2019) looked at the link between CAN and arterial stiffness, which was defined as an ABI of 1.2 or more, in people with T1DM while using vascular sonography to thoroughly check for aPAD [38]. The authors hereby report a relationship between cardiovascular autonomic dysfunction and peripheral artery compliance in young adults with T1DM who maintain acceptable glycemic control. Authors findings also show that the prevalence of CAN in patients with arterial stiffness is threefold higher than in patients with normal ABI values, with the highest prevalence in the subset of patients with both arterial stiffness and concomitant aPAD; in addition, this association persisted even after adjustments for the presence of other relevant cardiovascular risk factors and aPAD. Furthermore, in a cohort of patients with T1DM, peripheral arterial stiffness appears to foster the association of cardiovascular autonomic dysautonomia and atherosclerosis, suggesting another link between CAN and cardiovascular morbidity. Mounting evidence from others supports this dual pathogenic pathway from cardiac autonomic dysfunction to arterial stiffness and atherosclerosis. It seems that autonomic neuropathy is not only a microvascular complication, but several pathophysiological mechanisms are involved in its development [39, 40].

Genetic and epigenetic factors and CAN

Recent genetic studies have pointed to possible mechanisms that depend on inflammation, the immune system, or lipid abnormalities instead of intravascular pathways that control muscle contraction or mechanotransduction. It was first found that a common genetic variation in a locus in the

BCL11B gene desert was linked to higher PWV in the Aorta-Gen Consortium [41]. Examining the functional impact of selected single-nucleotide polymorphisms provided further evidence of the importance of common BCL11B gene desert variants. Correlations between the BCL11B transcripts and markers for activated lymphocytes suggest an immune-related mechanism in arterial stiffening [42]. A single-nucleotide polymorphism in the APOA5 gene is linked to higher PWV in people who have low HDL-C and low plasma adiponectin levels. This is an independent predictor of AS in people with T2DM or high blood pressure [43, 44].

Diabetes can cause or worsen neuropathy in many people. Some of the genes that were linked to this were ACE, MTHFR, GST, GLO1, APOE, TCF7L2, VEGF, IL-4, GPX1, eNOS, ADRA2B, GFRA2, MIR146A, and MIR128A [45]. Researchers focused some of their studies on determining the correlation between gene polymorphism and diabetic autonomic neuropathy. Examples of genes linked to autonomic dysfunction include the antioxidant enzyme glutathione S-transferase, the transcription factor TCF7L2 gene, and the ANS receptor alpha-2B-adrenergic receptor [18]. The role of genetic predisposition is now gaining some attention, given the finding of associations between CAN and polymorphisms of genes encoding a few microRNAs, i.e., MIR146a, MIR27a, and MIR499 [46]. MicroRNAs are posttranscriptional regulators of gene expression, implicated in various pathways and reported to be dysregulated in diabetes and its complications. In an Italian cohort of patients with T2DM, the C allele of the rs2910164 single nucleotide polymorphism in MIR146A was associated with a lower risk of developing CAN, whereas the variant allele of the rs895819 SNP in MIR27A was associated with a higher risk of developing early CAN [46]. Moreover, the analysis of the rs3746444 SNP in the MIR499A gene revealed that the MIR499A GG genotype, along with disease duration and HbA1c, contributes to early CAN. The GG genotype and disease duration are the main factors that contribute to the severity of CAN [46]. It is interesting to observe that microRNA-499 is preferentially expressed in the heart and areas of the central autonomic network (nucleus ambiguous) and is involved in both CVD and MetS/DM, as well as MIR499 polymorphisms that are in susceptibility to CVD [28, 46]. Within this theme, larger studies that evaluate the use of genetic markers in the prevention, diagnosis, treatment, and prognosis of the patient are still necessary [47].

Diabetes mellitus and circadian rhythms of HRV

Adaptation to stress is characterized by an increase in sympathetic activity and a decrease in parasympathetic activity, inducing a state of alertness [48]. Common diseases such as obesity and MetS, MI etc, are associated with a decrease in parasympathetic activity and an activation of sympathetic activity [49].

HRV reflects the changes in HR caused by fluctuations in sympathetic and parasympathetic function under steady conditions. Heart rate is never completely stable. Continuous tonic, phasic, and transient external and internal stimuli of multiple origins affect HR to a variable but measurable extent. Five different mechanisms have been described: sympathetic and parasympathetic efferences to the sinus node; neurohumoral influences (e.g., catecholamines, thyroid hormones); stretch of the sinus node; changes in local temperature; ionic changes in the sinus node. Under resting conditions, it can be assumed that the short-term HRV is essentially determined by the first and third factors. The sympathetic and parasympathetic stimuli directly influence HR and are responsible for a physiologic variation in the HR, or HRV. The HRV can be evaluated in the time and frequency domains [50, 51]. Time domain measures of the normal R-R intervals include the difference between the longest and shortest R-R intervals, the standard deviation of 5-min average of normal R-R intervals (SDANN), and the root-mean square of the difference of successive R-R intervals (RMSSD). Longer recordings (e.g., 24-h, classic 24-h Holter ECG) allow the calculation of additional indices, as the number of instances per hour in which two consecutive R-R intervals differ by more than 50 ms over 24 h (pNN50). Essentially, all these indices explore the parasympathetic activity [52, 53]. In the frequency domain, the use of spectral analysis of R-R interval (and other cardiovascular and respiratory signals) allows a precise description of the different fluctuations. The components of the HRV obtained by spectral analysis provide information about both the sympathetic and parasympathetic influences on the heart. Based on studies using acceptable techniques, there is evidence of reduced parasympathetic modulation of HR in diabetes and also reduced modulation of SBP in the low-frequency region [50, 51] particularly after sympathetic stimulation in response to tilting, or in the microcirculation. As most of the cardiovascular autonomic reflex tests (CARTs) essentially explore the parasympathetic activity, there is no other simple test of sympathetic activity capable of identifying early (functional or anatomic) autonomic sympathetic abnormality [54]. CARTs are considered the “gold” standard for CAN testing. Impaired HRV time- and frequency-domain indices have been reported in diabetic patients before CARTs abnormalities arise. However, the few studies that assessed the diagnostic accuracy against the reference standard of CARTs found only fair results. Time- and frequency-domain analysis of 24-h ECG recordings has documented an abnormal nocturnal sympathetic predominance in diabetic patients that was linked to BP non-dipping. In obese patients weight loss was associated with an improvement in global HRV and in parasympathetic HRV indices [4, 55].

In this way, HRV testing is a clinically relevant measure in addition to CARTs and provides key information about autonomic-parasympathetic and sympatheticmodulation of the cardiovascular system. Analysis of HRV can be done using statistical indices in the time and frequency domains. Time-domain indices of global HRV and total spectral power of HRV represent the index of parasympathetic activity, as well as the HRV spectral power in the high-frequency (HF) region, while the relative proportion (not the absolute power) in the low-freguency (LF) of HRV provides a relative measure of sympathetic modulation. This interpretation should be made with cautions if respiratory artifacts (slow breaths) cannot be excluded. Application of the technique is critically dependent upon understanding of the underlying physiology, the mathematical analyses used, and the many confounders and possible technical artefacts [4].

In early stages, CAN could be detected by decreased HRV with deep breathing, which implies parasympathetic dysfunction in patients with T2DM [56]. F. Olivieri et al. (2024) reported that HF power, as a direct measure of vagal nerve integrity, was reduced in early CAN in patients with T2DM [57]. Thus, frequency-domain measures of HRV might be a diagnostic method to detect early CAN in patients with T2DM [58]. Previous studies reported the association between impaired HRV and CAN in patients with and without T1DM and T2DM [4, 59].

The significant relationship between altered glucose metabolism and HRV may explain the deleterious general metabolic effects on both parasympathetic and sympathetic activity [60, 61]. Interestingly, blood glucose levels were associated with both an increase in LF (sympathetic) and HF (parasympathetic), as well as standard deviation of all normal RR (NN) intervals during a 24-h period (SDNN) (sympathetic) and RMSSD (parasympathetic), which may appear contradictory. In healthy individuals, parasympathetic activity is triggered by an increase in blood glucose levels through insulin responses [62].

Cardiovascular autonomic dysfunction results from damage to the nerves and blood vessels innervating the heart and can lead to dysfunctional HR control and abnormal vascular dynamics. Cardiac autonomic dysfunction is a frequent but underdiagnosed complication of T2DM that is associated with arrhythmia, MI, and sudden cardiac death [16]. One of the earliest subclinical manifestations of cardiac autonomic dysfunction is reduction in HRV with parasympathetic loss preceding sympathetic dysfunction [4, 63]. Compared with their peers without DM, adolescents with T2DM have early signs of cardiac and vascular abnormalities including left ventricular hypertrophy and diastolic dysfunction as well as vascular stiffness and thickness [64, 65]. However, cardiac autonomic function and HRV have been evaluated less frequently in young adults with youth-onset T2DM [66]. The SEARCH for Diabetes in Youth (SEARCH) study found cardiac autonomic dysfunction in 17 % of their cohort of young adults with youth-onset T2DM (compared with a lean control group), a higher prevalence than that seen in young adults with T1DM (17 vs 12 %) [36]. However, SEARCH was not able to identify risk factors associated with the presence of autonomic dysfunction, perhaps because of inadequate statistical power [64, 67].

Hyperglycemia is thought to be associated with abnormal signaling of autonomic neurons via accumulation of advanced glycation end products, activation of polyol pathway, and ischemia-induced atrophy of the autonomic nerve fibers innervating the cardiac and vascular tissue. Both divisions of the ANS are typically affected, with parasympathetic impairment preceding the sympathetic dysfunction [68, 69]. Loss of HRV is one of the earliest manifestations of this process. In the Framingham Heart Study, HRV was found to be inversely associated with the risk of mortality [70]. Similarly, the Atherosclerosis Risk In Communities study found decreased HRV was independently associated with the risk of developing coronary heart disease [71].

Another convincing point is that the relationships between HbA1c and HRV is logical. F. Li et al. (2023) demonstrated that higher levels of HbA1c were associated with shorter RR intervals, which were associated with an increased risk of ventricular arrhythmias. There was also a tendency for higher LF/HF ratio (i.e., decreased HRV) with higher levels of HbA1c [72]. Furthermore, time from diagnosis of T2DM was linked with a higher level of SDNN. J.-K. Chiang et al. (2024) demonstrated a decreased SDNN in T2DM patients; the meta-regression is not contradictory but may simply highlight the fact that cardiac parasympathetic activity in T2DM is affected before sympathetic activity. Time from diagnosis of T2DM was also linked with a lower level of total power, but not with LF and HF [73]. Thus T. Benichou et al. (2018) can hypothesize that very low-frequency (VLF) could be decreased in T2DM [62]. Despite few studies assessing VLF in DM, interesting relationships were reported between VLF and OSA in diabetics [74, 75].

Similarly, total cholesterol was associated with both an increase in LF and HF, and HDL-C was associated with an increase in SDNN and RMSSD [76]. Interestingly, some studies showed that a decrease in LDL-C by statin therapy could improve HRV parameters [62]. T. Benichou et al. (2018) demonstrated that an increase in SBP was linked with shorter RR intervals and a decrease in HF [62]. Despite no study previously assessing this relationship in DM, conflicting results were reported in the general population, with either high BP associated with an increase in all spectral parameters [77], or a decrease in HRV [78]. It has also been suggested that the decrease in autonomic nervous function precedes the development of clinical AH [79]. Moreover, T. Benichou et al. (2018) found a significant relationship between BMI and HRV [62]. Such relationships have been either found [80, 81] or not [82, 83]. However, the severity of obesity and related diseases is not directly linked to the accumulation of total body fat but rather to its distribution, and particularly to visceral localization [84]. HRV parameters have been previously correlated with sagittal abdominal diameter, anterior forearm skinfold thickness and waist hip ratio [62, 82].

Measuring HRV is challenged by environmental noise, mental stress, and physical activity during daytime [85]. Night-time HRV during sleep may be a more valid tool to measure CAN and therefore may improve prediction of CV events in low-risk people with T2DM [86]. Copenhagen Holter Study included 678 community dwelling subjects aged 55–75 yrs who were free of previous CVD. Day- and night-time HRV were available for 653 participants. The population included 133 people with well-controlled T2DM and newly recognized T2DM. Cardiovascular events were defined as CV death, MI, stroke, or coronary revascularization. 24-h HRV was not associated with CV events, but with all-cause mortality in people with T2DM. Conventional risk factors had a receiver operating characteristic value of 0.704 (95% CI 0.602–0.806) to predict CV events in people with T2DM. The prediction of CV events by conventional risk factors was improved in people with T2DM by the addition of night-time SDNN. Thus, reduced night-time HRV predicts increased risk of CV events in people with well-controlled T2DM, thus night-time HRV may add to traditional risk factors in predicting CV events in people with T2DM [87].

In T2DM's cardiac autonomic dysfunction, expressed as reduced vagal activity, leads to HR acceleration and thus to diastole shortening, but it seems that cardiac autonomic dysfunction may shorten diastole duration per se, independently

of the effect on HR [88]. Since diastole duration influences strongly subendocardial myocardial viability index, cardiac autonomic dysfunction plays a primary role in addition to arterial stiffness in the impairment of subendocardial myocardial viability index and may thus worsen CV prognosis [89]. S. Chorepsima et al. (2017) showed that beyond BP, impaired cardiac autonomic function assessed by determination of HRV was a significant determinant of abnormal pulse wave velocity (PWV) in patients with T2DM [90]. Furthermore, lower values of the frequency-dependent domains of the HRV were independently associated with higher odds of abnormal PWV [91]. It has been shown that low HRV is associated with increased mortality in patients with coronary heart disease or DM. HRV is also a sensitive indicator of BRS control, specifically the vagal control [51]. Therefore, arterial stiffness may affect BRS and thereby, HRV. Increased arterial stiffness evaluated by PWV and/or ambulatory arterial stiffness index has been associated with the presence of coronary atherosclerosis and worse CV prognosis both in general population and specific disease groups, including DM [92]. Decreased HRV in the uncomplicated diabetes patients highlights the obscure process of CAN in diabetic patients that begins even before clinical atherosclerotic CVD's becomes apparent [4, 93].

It has also been shown that surrogate atherosclerosis markers were associated with lower HRV, and increased carotid intima media thickness in T2DM participants was significantly associated with decreased HRV, independent from conventional CV risk factors. Therefore, the presence of CAN should be considered much earlier in the course of DM, rather than after the development of clinical CVD's (process of CAN in diabetic patients that begins even before clinical atherosclerotic CVD's becomes apparent) [4, 94]. Thus, there is strong evidence of a decrease in HRV in T2DM patients. Both sympathetic and parasympathetic activities were decreased, which can be explained by the deleterious effects of altered glucose metabolism on HRV [62]. The benefits of an HRV evaluation in assessing and monitoring the severity of T2DM should be further studied, given its potential as a noninvasive, reliable and pain free measurement.

Diabetic CAN and circadian rhythm disorders

Cardiac autonomic neuropathy is a significant risk factor for cardiovascular injury resulting in heart attack, congestive heart failure, stroke and sudden arrhythmic death. This issue is associated with myocardial structural remodeling that follows AH, such as hypertrophy and fibrosis. This remodeling accompanies changes in expression, distribution, and function of cell membrane ion channels, Ca^{2+}-cycling proteins, intercellular gap junction connexin-43 channels and extracellular matrix composition [4, 95].

There is a lot of evidence that CAN plays a crucial role in the pathogenesis of progressive vessel atherosclerosis [18, 38, 96]. Moreover, diabetic autonomic neuropathy is closely associated with subclinical myocardial dysfunction, interstitial myocardial fibrosis, and metabolic changes [67]. Additionally, CAN also significantly increases the incidence of CVD's and their related mortality [97]. However, the independent relationship of CAN with the severity of coronary lesions in T2DM patients has not been established [97, 98].

A new CVD's risk factor, which could be more helpful in terms of prognosis in particular, "syndrome of vascular aging", is needed and the possibility of its using is actively discussed. The results of several epidemiological studies reported that increased arterial stiffness predicts mortality and morbidity, independently of other CV risk factors. Additionally, results from clinical studies have shown that arterial stiffness increases with aging or several pathological conditions associated with AH, MetS, chronic kidney disease, and DM [90]. Diabetes may increase arterial stiffness through pathological changes in the vascular bed, such as changes in structure or type of elastin and/or collagen in the arterial wall, chronic low-grade inflammation, increased OS, reduced nitric oxide bioavailability, increased activity of SNS [99, 100].

Cardiac autonomic dysfunction has been considered as a significant risk factor in the acceleration of atherosclerosis and serves as a trigger for cerebrovascular or CV events. The pathophysiology of CAN is complex and involves the endocrine and vegetative nervous system with associated metabolic, inflammatory and hemostatic abnormalities [101]. The pathophysiological link between autonomic dysfunction and aortic stiffness and whether impaired cardiac autonomic function induces the arterial stiffness or increased arterial stiffness leads to autonomic function's impairment remains obscure. Both the arterial stiffness and cardiac autonomic dysfunction share common pathogenetic pathways including chronic hyperglycemia and IR, formation of advanced glycation end products and protein kinase C activation, low grade-inflammation and ED [90]. Insulin resistance and HI increase systemic metabolic disorders and activate the SNS; then activate renin-angiotensin-aldosterone system; prompt OS, mitochondrial dysfunction, and endoplasmic reticulum stress; and impair Ca^{2+} homeostasis. These effects result in cardiac fibrosis, hypertrophy, cardiomyocyte death, dysfunction of the coronary microcirculation, and eventually heart failure [4, 102].

Conclusions

CAN is one of the underdiagnosed microvascular complications of T2DM caused by hyperglycemia-induced neuronal damage. The decline in HRV is seen even before manifesting signs and symptoms of diabetic CAN. As a result, there is strong evidence of decreased HRV in T2DM patients. HRV pattern analysis has the capacity to discover autonomic imbalance in the preclinical and asymptomatic stages. Both sympathetic and parasympathetic activity is reduced in T2DM persons, which can be explained by the negative effects of altered glucose metabolism on HRV. Arterial stiffness may contribute to cardiovascular dysautonomia by inducing baroreceptor dysfunction; conversely, CAN may favor arterial stiffness by increasing HR and impairing arterial wall elasticity. Both states may also develop in parallel due to aging in the presence of hyperglycemia. The presence of CAN should be evaluated considerably earlier in the DM process, and reduced HRV is the earliest sign of CAN. Improvement of HRV may allow guiding the patients toward lifestyle changes and early management. Given its promise as a noninvasive, reliable, and painless assessment, the benefits of an HRV evaluation in diagnosing and monitoring the severity of T2DM should be investigated further.

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Порушення циркадних ритмів варіабельності ритму серця при діабетичній кардіальній автономній нейропатії: механізми та наслідки

Резюме. Порушення варіабельності ритму серця (ВРС) може збільшити ризик серцево-судинних захворювань протягом наступних шести років від 4 до 100 %. Повідомляється, що хронобіологічна оцінка ВРС та своєчасна оптимізація лікування дозволяють зменшити ризик інсульту або серцевої смерті. Фізіологічна серцево-судинна діяльність знаходиться під контролем вегетативної нервової системи. Пошкодження вегетативних нервів викликає порушення контролю частоти серцевих скорочень і судинної динаміки, особливо при кардіальній автономній нейропатії (КАН). Вегетативний дисбаланс у регуляції серцево-судинної функції симпатичною (СНС) та парасимпатичною нервовою системою (ПСНС) призводить до метаболічних порушень і значної захворюваності й смертності серед осіб із цукровим діабетом (ЦД). У них виявляють порушення циркадних ритмів. Існує тісний зв'язок між змінами нейроендокринної архітектури сну, коливаннями біологічного годинника, метаболізмом глюкози, вегетативною функцією та добовими профілями артеріального тиску й частоти серцевих скорочень. Метаболічний синдром, артеріальна гіпертензія, інфаркт міокарда та ЦД характеризуються підвищеною активністю СНС і зниженою — ПСНС. Однак у хворих на ЦД 2-го типу спостерігається зниження активності як ПСНС, так і СНС. Це можна пояснити тим, що ЦД 2-го типу є метаболічним захворюванням, яке спричиняє КАН, вражаючи симпатичні й парасимпатичні волокна. Метою цього огляду було обговорення сучасного стану проблеми взаємозв'язку ЦД і порушень циркадного ритму, ВРС. Особливу увагу приділено факторам ризику діабетичної КАН; механізмам збільшення смертності, пов'язаної з КАН; патогенезу діабетичної КАН; можливим патогенетичним шляхам, що пов'язують КАН та прогресування атеросклерозу; генетичним, епігенетичним особливостям і КАН; ЦД та циркадним ритмам ВРС; діабетичній КАН і порушенням циркадного ритму ВРС. Пошук проводився в Scopus, Science Direct (від Elsevier) і PubMed, включно з базами даних MEDLINE. Використані ключові слова «цукровий діабет», «кардіальна автономна нейропатія», «циркадні ритми», «варіабельність ритму серця». Для виявлення результатів досліджень, які не вдалося знайти під час онлайн-пошуку, використовувався ручний пошук бібліографії публікацій.

Ключові слова: цукровий діабет; кардіальна автономна нейропатія; циркадні ритми; варіабельність ритму серця; огляд літератури

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