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Type 2 Diabetes Mellitus: Cardiovascular Autonomic Neuropathy and Heart Rate Variability

Sultana Ferdousi and Phurpa Gyeltshen

Abstract

Type 2 Diabetes Mellitus is associated with both macro- and microvascular complications. One among the latter, is cardiovascular autonomic neuropathy (CAN). CAN is attributed to cardiac arrhythmias and sudden death. Underlying pathogenesis of cardiac autonomic neuropathy is chronic hyperglycemia induced oxidative stress causing neuronal necrosis, apoptosis and death, leading to the sympathetic and parasympathetic nerve dysfunction. The balance between sympathetic and parasympathetic nervous system is reflected by heart rate variability (HRV). HRV describes “the variations of both instantaneous heart rate and R-R intervals which in turn reflects the cardiac autonomic nervous control”. HRV measured at rest is a marker of autonomic nerve function status. Thus, HRV test is recommended to diagnose diabetic CAN. Time domain parameters predominantly reflect overall autonomic activity and parasympathetic nervous system (PNS) modulations. Frequency domain parameters either reflect, sympathetic nervous system (SNS) activity, PNS activity, or the balance between the two activities. Nonlinear HRV indices marks PNS influences, SNS influences and sympatho-vagal balance. Almost all these HRV parameters are remarkably reduced in T2DM due to cardiac autonomic dysfunction. HRV is an important simple and noninvasive diagnostic tool to detect CAN.

Keywords: type 2 diabetes mellitus, oxidative stress, heart rate variability, cardiac autonomic neuropathy, time domain, frequency domain

1. Introduction

Diabetes mellitus “is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both” [1]. World Health Organization (WHO) estimated that about 422 million of global population were suffering from diabetes mellitus in 2014 [2]. This number is estimated to have reached to more than 500 million in 2018 [3]. From the total diabetes mellitus population, 90–95% belongs to T2DM category [4].

T2DM is associated with both acute and chronic complications: microvascular and macrovascular complications [5]. Diabetic autonomic neuropathy (DAN) is one of the microvascular complications [6]. DAN causes autonomic dysfunction

of many organs and cardiovascular autonomic dysfunction due to diabetic CAN is the most life-threatening condition [7]. Thus, CAN has been found associated with cardiac arrhythmias, silent myocardial infarction and sudden deaths in T2DM patients [8]. CAN progresses through a prolonged subclinical to clinical form [7, 9]. Clinical CAN or late stage CAN occurs due to both parasympathetic and sympathetic denervation of heart and it may be manifested by resting tachycardia, orthostatic hypotension, exercise intolerance and silent myocardial ischemia. But subclinical or early stage CAN is characterized by predominant damage to the vagus nerve innervating the heart with subsequent upper hand in sympathetic drive resulting in resting cardiac autonomic balance characterized by resting tachycardia [9]. However, sub-clinical CAN ensues largely from functional alteration of autonomic nerves and is considered a reversible disorder [10].

Reduced HRV is the earliest sign of subclinical CAN [11]. HRV refers to a variation of RR intervals in time [12, 13]. HRV measured at rest is a marker of autonomic balance as well as cardiac sympathetic and parasympathetic tonic activity [13]. HRV is assessed through time domain, frequency domain and nonlinear metrics of electrocardiogram (ECG) recording [13]. HRV is reduced in type 2 diabetic patients with CAN compared to those without CAN [14].

2. Autonomic nervous system regulation of cardiovascular functions

Autonomic nervous system (ANS), a portion of peripheral nervous system, has two subdivisions viz. sympathetic and parasympathetic nervous system. They are responsible for regulating the functions of almost organs of the body via visceral reflexes. Centrally, ANS activities or reflexes are integrated and controlled by hypothalamus, brain stem and spinal cord. Heart and blood vessels are innervated by sympathetic and parasympathetic nerve fibers. Thus, their functions are largely regulated by ANS apart from other regulating factors to adapt to different short-term or long-term physiological/pathological changes of the internal environment of the body.

2.1 Regulation of cardiac functions

The main function of the heart is to pump blood into the closed circuit of circulation. The efficiency of this mechanical property of the heart depends on normal electrophysiology of the heart which per se depends on normal structural and functional integrity of sinus atrial node (SA node) and rest of the conducting system of the heart. Autonomic nervous system plays crucial role in controlling both electrical and mechanical properties of the heart. However, the degree of influence of sympathetic and parasympathetic nerves on heart functions depends on their abundance of innervation in different parts of the heart.

Sympathetic nervous system via right and left cardiac nerves innervate atria and ventricles (including conducting system). Right cardiac nerve predominantly innervates SA node and it has more influence on heart rate (HR) and on the other hand left cardiac nerve predominantly controls myocardial contractility. Thus, the net effect of sympathetic stimulation is to increase HR, conduction velocity and strength of myocardial contractility. Parasympathetic nervous system through right and left vagus nerves innervate predominantly atrial muscle and very sparsely ventricular myocardium. Right vagus nerve primarily innervates the SA node and left vagus nerve innervates mainly atrio-ventricular node (AV node). Thus, the net effect of parasympathetic stimulation is to decrease HR and slightly decrease strength of heart contractility. Dynamic interaction occurs between sympathetic

and parasympathetic divisions. However, during rest, parasympathetic tone predominates over sympathetic tone. Therefore, resting HR is mainly controlled by the vagal nerve tone [15]. Hence, resting HR is a marker of vagal nerve function status [15].

2.2 Regulation of vascular functions

Arteries and veins are innervated only by sympathetic nerve fibers, whereas, capillaries do not have any autonomic nerve innervation. Thus, vasomotor tone of almost all blood vessels is mainly determined by sympathetic tone. Sympathetic stimulation causes vasoconstriction and vice versa. Parasympathetic nerve fibers do innervate some blood vessels of salivary glands, gastrointestinal glands and genital erectile tissues.

3. Diabetic autonomic neuropathy

DAN is quite common, yet remained mostly undiagnosed and micro-vascular complications of T2DM are affecting many organ systems (gastrointestinal, genitourinary, cardiovascular) of the body [7]. However, CAN is clinically the most important form of DAN as it is associated with life-threatening complications (arrhythmias, silent MI) and sudden death [9]. The underlying pathophysiology of DAN is still unclear; however, it has been attributed to chronic hyperglycemia induced oxidative stress and inflammation with subsequent neuronal injury and death [9, 16–19].

3.1 Hyperglycemia induced oxidative stress and inflammation

Oxidative stress and inflammation are interlinked, as one causes another and vice versa, and they occur even under normal physiological conditions. However, these two phenomena last for a brief period as they are suppressed by intrinsic negative feedback mechanisms; increased production of antioxidants and anti-inflammatory cytokines [19]. But, in certain chronic diseases like T2DM these altered states of internal environment sustain for a prolonged period as positive feedback mechanisms overrides the negative feedback mechanisms [19]. In addition, reduced parasympathetic nerve function due to autonomic dysfunction in T2DM leads to chains of inflammatory responses [20]. Thus, oxidative stress and inflammation are very prominent features in T2DM linked to both microvascular and macrovascular complications associated with T2DM [19]. Certain cells are particularly susceptible to hyperglycemic induced injury as their intracellular glucose concentration increases in a linear fashion with respect to the extracellular glucose level [16]. This is especially true for endothelial cells and neurons as the transport of glucose through their cell membranes is mediated by insulin-independent GLUTs [16].

Hyperglycemia induces overproduction of mitochondrial superoxide in endothelial cells of large and small blood vessels and neuronal axons [9, 16]. This leads to intracellular accumulation of reactive oxygen species (ROS) with subsequent activation of five major metabolic pathways: polyol pathway flux, increased formation of advanced glycation end-products (AGEs), increased expression of the receptor for AGEs and its activating ligands, activation of protein kinase C (PKC) isoforms, and overactivity of the hexosamine pathway [9, 16]. Over activity of these five metabolic pathways leads to accumulation of toxic metabolic derivatives and pro-inflammatory substances, bringing about following consequences: vascular

endothelial damage, vasoconstriction, neuronal hypoxia, neuronal cell necrosis, neuronal apoptosis and axonal degeneration (**Figure 1**) [9, 16, 19, 21, 22].

3.2 Cardiovascular autonomic neuropathy

CAN defined as the “impairment of autonomic control of the cardiovascular system in the setting of diabetes after exclusion of other causes” [23]. The prevalence of CAN varies from 31–73% in T2DM patients [17]. The T2DM patients with a higher age, longer duration of diabetes, poor and perhaps unstable glycaemic control, comorbid diabetic polyneuropathy, retinopathy and nephropathy, hypertension (on treatment), and other cardiovascular risk factors (in particular obesity and metabolic dyslipidaemia) are high risk of developing CAN [24].

CAN results from impairment of autonomic regulation on heart and blood vessels with consequent alteration of cardiovascular hemodynamic functions [20]. Underlying pathogenesis of CAN first damages longest autonomic nerve. Thus, CAN initially (subclinical CAN) begins with reduced parasympathetic control, as vagus is the longest autonomic nerve, with the consequent sympathovagal imbalance. Hence, reduced HRV is the earliest marker of CAN [20]. Subclinical CAN be even seen in prediabetes [24]. As subclinical CAN progresses

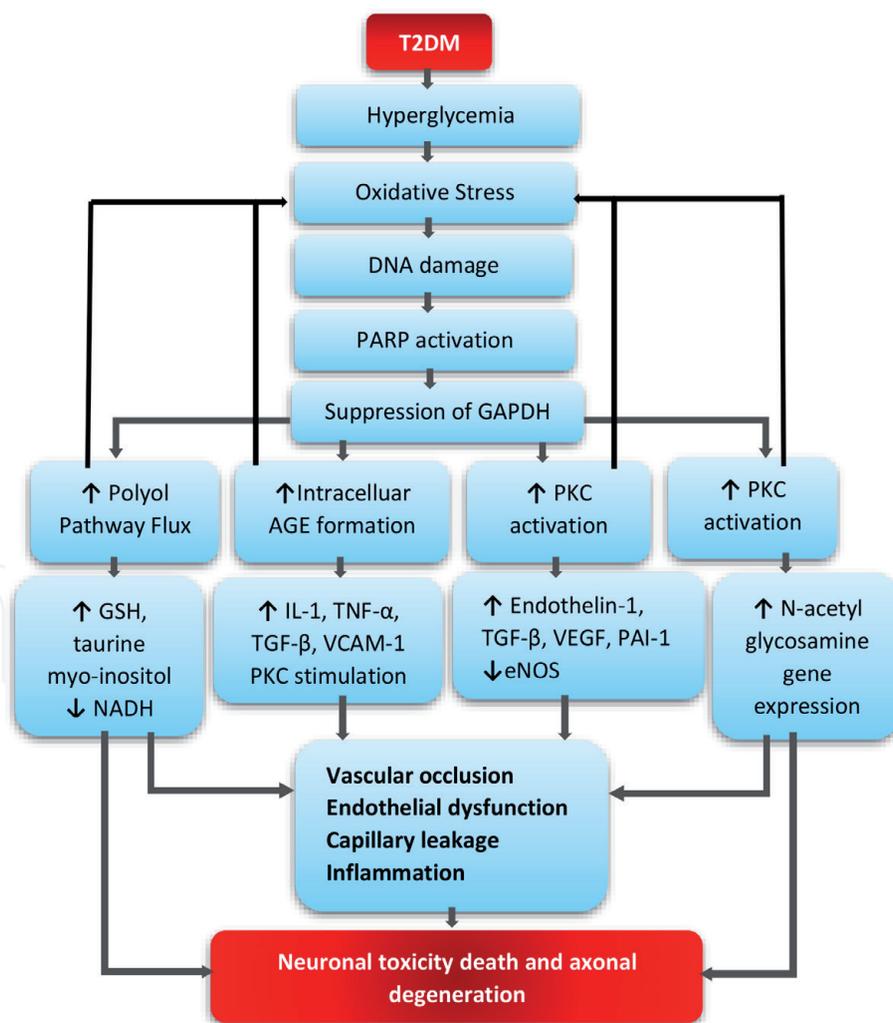


Figure 1.

Summary of the mechanisms that relate hyperglycemia to microvascular complications in patients with diabetes [9, 15, 18, 20, 21]. PKC: Protein kinase C; AGE: Advanced glycation end-products; GAPDH: Glyceraldehyde-3 phosphate dehydrogenase; GSH: Glutathione; NADH: Nicotinamide adenine dinucleotide; TGF-β: Transforming growth factor; VEGF: Vascular endothelial growth factor; PAI-1: Plasminogen activator inhibitor-1; eNOS: Endothelial nitric oxide.

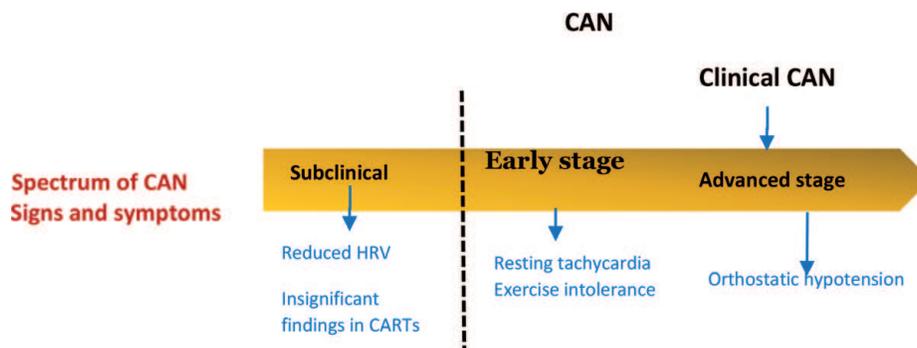


Figure 2.
 Progression of CAN with signs and symptoms [9, 22].

into clinical CAN, sympathetic tone augments during early stage and followed by sympathetic denervation in later stage (Figure 2). This denervation begins at the apex of the heart and advances towards the base of the heart. This disproportionate sympathetic denervation of ventricles predisposes to the development of cardiac arrhythmias. CAN is also associated with silent myocardial infarction (MI) and sudden death. CAN is highly associated with cardiovascular morbidity and mortality and thus, it is crucial to be diagnosed at its early stage to prevent these complications [25].

Clinical CAN is usually diagnosed and its severity is assessed by autonomic score obtained through five standard cardiovascular autonomic reflex tests (CARTs): (1) the HR response to deep breathing (2) the HR response to standing (3) the Valsalva maneuver (4) the blood pressure response to standing and (5) the blood pressure response to sustained handgrip [26]. Whereas, subclinical CAN is diagnosed based on changes in HRV, baroreflex sensitivity, and cardiac imaging showing increased torsion of the left ventricle [26]. Sensitivity of standard CARTs to detect subclinical CAN is very limited as no significant changes are seen on standard CARTs [26]. Detecting CAN at subclinical stage is of paramount importance to provide early intervention on modifiable risk factors of CAN to prevent progression CAN to its severe or advanced form [24, 26].

4. Heart rate variability

Heart rate is controlled by changes in sympathetic and parasympathetic influences, neurohumoral factors (epinephrine and thyroid hormones), ionic concentrations (calcium and potassium) and local temperature of SA node [27]. But, the HRV measured over short period of time (5 minutes) at rest is largely determined by changes of autonomic nervous system control (predominantly by the vagal tone) and the stretch of SA node [22]. On the contrary, long-term measurement of HRV obtained through 24-hour Holter ECG can be influenced by concomitant illness, use of medications, and lifestyle factors (exercise, stress, smoking, etc.) in addition to afore mentioned factors [22]. HRV is also varies due to other physiological factors (Table 1). Short-term HRV (5 minutes) measurement is a reliable technique to detect autonomic dysfunction [9]. HRV describes the variations of both instantaneous heart rate and RR intervals which in turn reflect the cardiac autonomic nervous control (Figure 3) [13]. HRV measurement obtained from 5 min-ECG recording represents marker for the measurement of resting autonomic tonic activity; the balance between sympathetic & parasympathetic nervous activity at any instant. Thus, alteration of HRV can detect the impairment of resting sympathetic and parasympathetic activity individually and shift of the normal sympathovagal

Physiological factors influencing on HRV		
• Age	• Circadian rhythm	• Body position
• Gender	• Respiration	• Physical fitness
• Food ingestion	• Body mass index	

Table 1.
Physiological factors to be considered while measuring HRV.

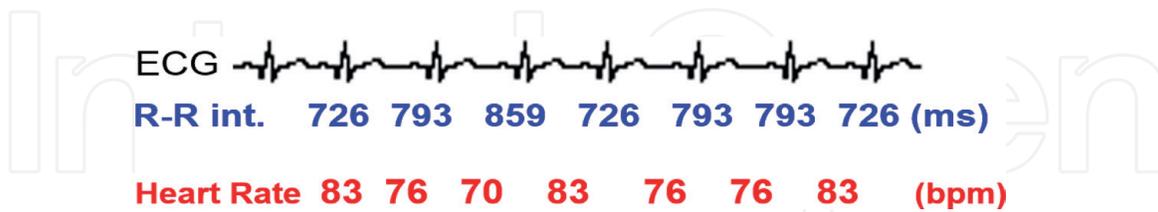


Figure 3.
Heart rate variability (HRV). Ms: Milliseconds, bpm: Beats per minute, R-R int.: R-R interval.

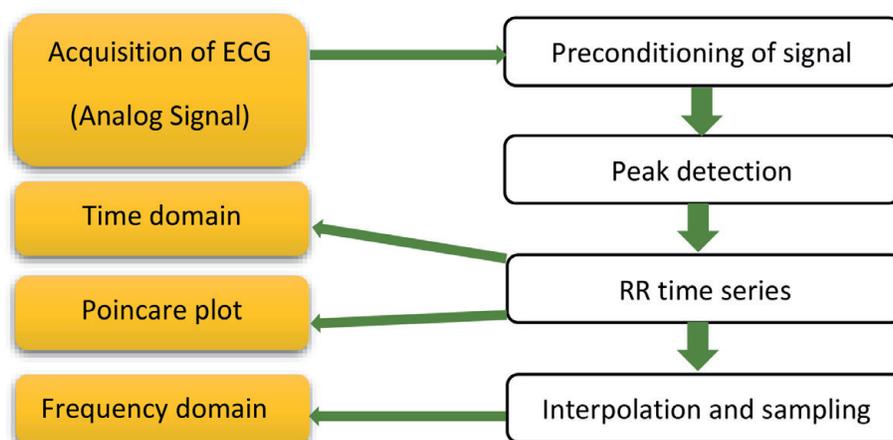


Figure 4.
Quantification of HRV into time domain and frequency parameters along with Poincare plot.

balance. HRV is quantified or measured by three methods; time domain, frequency domain and nonlinear analysis of short-term (5 mins) and long-term ECG (24 hrs.) recording (**Figure 4**). HRV test is an accurate quantitative and reproducible measurement of autonomic nerve function [13].

4.1 Time and frequency domain, and non-linear analysis of HRV

The time domain method measures the heart rate at any point either in time or in the intervals between successive QRS complex of a continuous ECG record. The interval between adjacent QRS complexes is known as normal-to normal (NN) interval. HRV time-domain indices quantify the amount of HRV observed during monitoring periods that may range from <1 min to >24 h. Time domain variables include the SDNN, SDANN, SDNNI, RMSSD, NN50, pNN50, HR Max – HR Min (**Table 2**) [28] (**Figure 5**).

Frequency domains variables (**Table 3**) are derived through many methods. Fast Fourier Transformation (FFT) is one the commonest methods to derive frequency components of HRV. Power spectrum derived through FFT is subsequently categorized into different bands of frequencies: VLF- (0.0033 to 0.04) Hz, LF- (0.04 to 0.15) Hz and HF- (0.15 to 0.4) Hz. Power spectral densities (PSD) are then plotted

Variable	Unit	Description	Physiological correlates
SDNN*	Ms	Standard deviation of NN intervals	Reflects PNS function
SDANN	ms	Standard deviation of the average NN intervals for each 5 min segment of a 24 h HRV recording	“
SDNN index	Ms	Mean of the standard deviations of all the NN intervals for each 5 min segment of a 24 h HRV recording	“
NN50	Ms	Number of R-R interval differences ≥ 50 ms	“
pNN50	%	Percentage of successive RR intervals that differ by more than 50 ms	“
RMSSD	Ms	The Root square of the mean of the sum of the squares of differences between adjacent RR intervals.	“
Max HR-Min HR	Bpm	The average difference between the highest and lowest HRs during each respiratory cycle	Mediated by RSA

*It is more accurate when measured from 24 h-ECG recording than that measured from shorter period.
 “Reflects PNS function. RSA: respiratory sinus arrhythmia. Bpm: beats per minute. PNS: parasympathetic nervous system.

Table 2.
 Time domain variables of HRV with physiological significance.

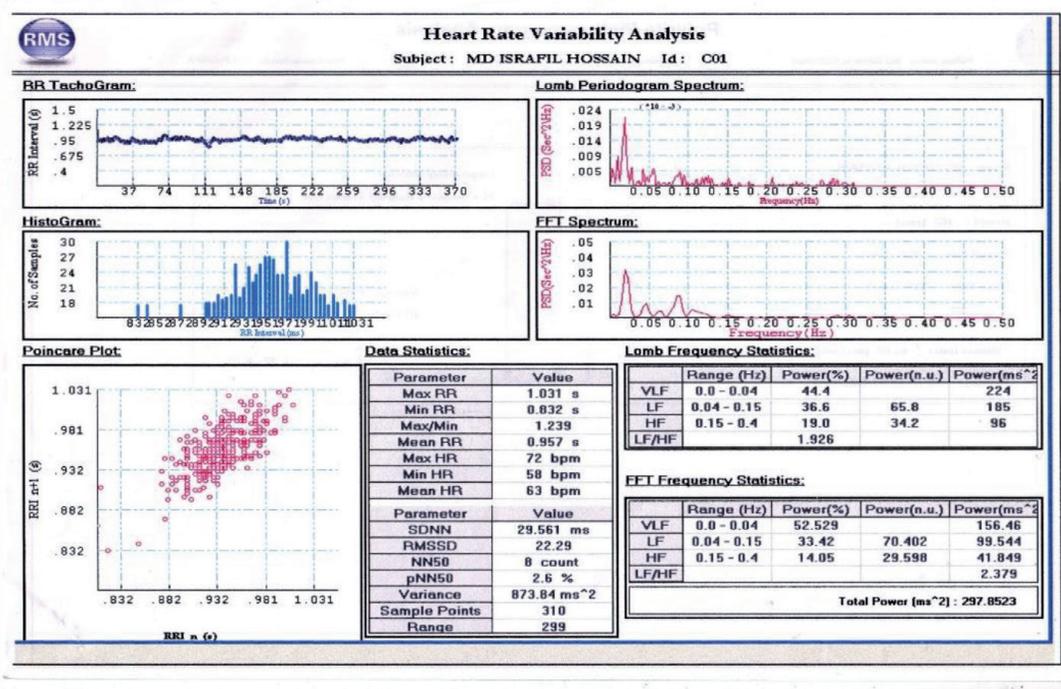


Figure 5.
 Time domain, frequency domain measurements and Poincare plot of HRV obtained through RMS Polyrite.

in ms²/Hz against preset frequencies. Power of the spectral bands are calculated in ms² (absolute power) and in normalized units (n.u). For example, normalize unit of LF is calculated by the formula: [LF/total power-VLF] × 100. Power of LF and HF are established in short term analysis of HRV. Nonlinear method of HRV analysis (Table 4) through Poincare plot is done by plotting every RR interval against the prior interval consequently forming a scatter plot.

Variable	Unit	Description	Physiological correlates
*VLF power	ms ²	Absolute power of the very-low-frequency band (0.0033–0.04 Hz)	Mediated renin-angiotensin system
LF peak	Hz	Peak frequency of the low-frequency band (0.04–0.15 Hz)	PNS and SNS influences
LF power	ms ²	Absolute power of the low-frequency band (0.04–0.15 Hz)	“
LF power	Nu	Relative power of the low-frequency band (0.04–0.15 Hz) in normal units	“
HF peak	Hz	Peak frequency of the high-frequency band (0.15–0.4 Hz)	PNS influences
HF power	ms ²	Absolute power of the high-frequency band (0.15–0.4 Hz)	#
HF power	Nu	Relative power of the high-frequency band (0.15–0.4 Hz) in normal units	#
LF/HF	%	Ratio of LF to HF power	Sympatho-vagal balance

**It is not well defined in short-term recording.*
“PNS AND SNS influences.
#PNS influences.

Table 3.
Frequency domain variables of HRV with physiological significance.

Variable	Unit	Description	Physiological correlates
SD1	Ms	Poincaré plot standard deviation perpendicular the line of identity	PNS influences
SD2	Ms	Poincaré plot standard deviation along the line of identity	SNS influences
SD1/SD2	%	Ratio of SD1- to – SD2 power	Sympatho-vagal balance

Table 4.
Non-linear variables of HRV and physiological significance.

4.2 HRV in type 2 diabetes mellitus

Reduced HRV is the earliest of sign CAN, reflecting impaired sympathetic and parasympathetic activity without apparent clinical signs and symptoms of CAN [29]. T2DM causes decrease in almost all HRV variables. In a systematic review and meta-analysis performed on 25 studies analyzing HRV in T2DM showed overall decrease in the HRV in patients with T2DM owing to reduction both sympathetic and parasympathetic nerve function [30]. In another systematic review done on eight studies showed SD1/SD2, SDANN, and HF to have more sensitivity and specificity to detect autonomic dysfunction in diabetic patients indicating their potentials to be better diagnostic markers [31].

Abnormal nonlinear HRV variables are associated with diabetes or with the risk of development of T2DM [32]. Likewise, a review study revealed reduction in HRV variables, obtained through short-term and 24-hour ECG recording, in metabolic syndrome and T2DM [29].

There are no standard reference values for HRV variables to diagnose CAN [22]. However, Breder and Sposito proposes the diagnosis of CAN could be made on obtaining abnormal result in at least two of the following six parameters:

SDNN <50 ms, RMSSD <15 ms, PNN50 < 0.75%, LF < 300 ms², HF < 300 ms² derived from 24-hour Holter ECG recording [33].

5. Conclusion

HRV displays beat-to-beat variations caused predominantly by the interplay of PNS and SNS control on SA node. Decline in HRV is seen even before manifesting signs and symptoms of diabetic CAN. Reduced HRV is the earliest sign of CAN. CAN is one of the under diagnosed microvascular complications of T2DM caused by hyperglycemia induced neuronal damage. Almost all HRV variables are decreased in T2DM.

Conflict of interest

The authors declare no conflict of interest.

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