Abstract

Epidemiological studies show an emergence of diet- and lifestyle-related diseases; Cardio-metabolic diseases (CMD) and neuropsychiatric diseases (classified as non-communicable diseases or chronic diseases). Diet and lifestyle factors can cause adverse effects on autonomic function resulting in decreased heart rate variability (HRV). Low HRV is a risk factor for CMDs. There is a need to find out new methods of early diagnosis for prevention and treatment of these problems because the neurohormonal dysfunction could be the earliest manifestation. It is possible that HRV could be a marker for the early diagnosis of these problems, because it is characterised with increased sympathetic and reduced parasympathetic activity. Several studies indicate that increased unhealthy diet, mental stress, sedentary lifestyle, tobacco, insomnia and alcoholism may be associated with neurohormonal dysfunction, which may cause decline in HRV. Majority of the chronic diseases (e.g., diabetes, hypertension, heart attack, neuropsychiatric disease and cancer) are associated with decreased HRV. The studies also indicate that solar and geomagnetic activities may influence circadian clock and hypothalamus resulting in the oxidative stress and inflammation with alteration in HRV. It is possible that reduced HRV will correlate with various stages of autonomic dysfunction, associated with chronic diseases. Simple methods need to be developed to measure HRV for early diagnosis of neurohormonal dysfunction, which may be important for early management. This review aims to find out available evidence on the role of HRV in the early diagnosis of chronic disease (with specific focus on Type 2 diabetes) and the factors affecting HRV.

Keywords: Catecholamines, chronic disease, heart rate variability, inflammation, psychosocial stress, Type 2 diabetes

Introduction

Chronic diseases, such as cardiovascular disease (CVD), stroke, diabetes, cancer and chronic respiratory diseases may be related to neuropsychiatric diseases.[1-3] The progression of chronic disease is triggered by multiple risk factors related to the lifestyle and the environment (physical inactivity, obesity, alcohol, tobacco, chronic stress, insomnia, etc.) resulting in changes in pathophysiology.[4] Specifically, the journey towards any chronic disease begins with signs of autonomic dysfunction, metabolic syndrome (MetS), insulin resistance (e.g., diabetes) and the chronic disease itself followed by the complications (e.g., neuropathy for diabetes). There is a need for early diagnosis and prevention during this journey towards the chronic disease. The aim of this review is to study the available evidence in the area of Type 2 diabetes (T2D) and heart rate variability (HRV) to understand (a) is HRV a meaningful marker for T2D risk, the disease progression and its complications? (b) Can HRV be leveraged to understand the mortality risk and comorbidities associated with T2D? and (c) Which factors affect HRV (e.g., insomnia, obesity and other lifestyle choices) that could become part of the clinical discussions and the interventions?

Heart Rate Variability

HRV is a key indicator of the sympathetic and the parasympathetic nervous system activity and the autonomic imbalance is often caused by increased sympathetic activities.

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and/or reduced parasympathetic activities. Improvement in HRV may be associated with autonomic nervous system (ANS) homeostasis and decreased HRV indicates the imbalance in autonomic tone. Therefore, there is an opportunity to identify a non-invasive marker that may be an indicator of future risk of cardiometabolic diseases (CMDs) and chronic diseases in general. Studies have also indicated that HRV at frequencies lower than respiration in humans appears to occur in synchrony with arterial pressure (Mayer waves) at a frequency close to 0.10 Hz (a 10 s rhythm). In other words, there are two primary rhythmic oscillations that underline the complexity of the heart rate waveform, the first oscillation occurs over several cardiac cycles is respiratory related, termed respiratory sinus arrhythmia and the second oscillation occurs at approximately 10 s cycle. It is likely that advancement in technology and analytical methods can enable us with greater in-depth analysis of the HRV that may enhance our exiting capability in the early diagnosis of the risk of disease with focus on T2D for this review. Various factors governing HRV are presented in Figure 1. To quote from the Fatisson et al.: “The direction of the arrows indicates a cause-to-effect link between related factors. While red arrows indicate a deleterious effect and green or blue arrows a beneficial one, purple arrows refer to a link for which the effect can be deleterious or beneficial. Blue arrows are specific to the heart coherence state, green and blue arrows correspond to significant effects while grey arrows indicate a link for which statistical significance was not achieved”.

**Measurement of Heart Rate Variability**

The European task force defined the standards for the measurement of HRV. It contains guidelines for signal acquisition [e.g., using electrocardiogram (ECG) or a device that measures RR intervals], sampling frequency range, pre-processing guidelines, duration of the recording, analysis methodology, etc. Time domain analysis is the easiest and more commonly used approach. It measures various parameters such as RR or NN interval (in ms – milliseconds), its standard deviation called standard deviation of all normal-to-normal RR intervals (SDNN), heart rate, RMSSD (square root of the mean of the sum of squares of differences between adjacent RR intervals), NN50 (number of pairs of adjacent RR or NN intervals differing by more than 50 ms in all measurements) and so on. Frequency domain employs fast fourier transform algorithm to provide amplitudes of the frequencies present. Results also include power spectrum data showing the power versus the frequency and non-linear analysis. For further understanding, reader is encouraged to explore the reviews providing insights on the measurement and watch-outs related to HRV. Limitations of HRV analysis and measurements are covered at the end of the review.

**The Challenge of Chronic Diseases and its Complications**

T2D is a multifactorial disease and may be associated with MetS characterised by altered glucose metabolism that can affect

![Figure 1: Influence diagram of cause of effect factors linked with heart-rate variability (HRV). (Included with permission from the author: Fatisson et al)](image-url)
organ function either directly or indirectly through oxidative stress and inflammatory mechanisms linked to hyperglycaemia, increase in free fatty acids, triglycerides and methylglyoxal with a deficiency of endogenous antioxidants; superoxide dismutase, catalase, ceruloplasmin and antioxidant nutrients. Free radical stress and inflammation are considered as the main causative factors of diabetes and its complications including renal, retinal, vascular and neurological impairments. However, the mechanisms for the development of complications due to diabetes are multifactorial. Apart from diet and lifestyle factors causing oxidative stress and inflammation, environmental factors and genetic predisposition may also contribute in the development of complications.

Specifically, the complications of T2D mellitus (T2DM) do not always occur in isolation but are often found as a group in patients, particularly among those with uncontrolled blood glucose and most often involve autonomic dysfunction. All the organs of the body are modulated by the ANS and ANS dysfunction is a major cause of increased morbidity and mortality in T2D. Approximately half of the patients with nephropathy attending secondary and tertiary care, experience autonomic impairment and cardiomyopathy. Retinopathy has been associated with cardiac autonomic dysfunction in both type 1 and T2DM patients. Peripheral vascular disease and peripheral neuropathy have also been associated with symptoms of distal sympathetic autonomic neuropathy. The sympathetic and parasympathetic components of the ANS are both affected by increased blood glucose levels, oxidative stress and inflammation, leading to multiple organ dysfunction and cardiac autonomic neuropathy (CAN). CAN is characterised by an altered cardiac rhythm due to the initial changes in the parasympathetic system, followed by sympathetic modulation of the cardiac rhythm as well as blood pressure and blood glucose variations.

Meta-analyses of published data have demonstrated that reduced cardiovascular autonomic function as measured by HRV is strongly (i.e., relative risk is doubled) associated with an increased risk of silent myocardial ischaemia and mortality in diabetes patients. The exact cause of how single or multiple diabetic complications (e.g., nephropathy and retinopathy) influence cardiac autonomic dysfunction is unknown. It would be useful to understand how HRV and the journey into diabetes continuum relate to each other.

Factors Affecting the Autonomic Imbalance

Epidemiological studies have indicated that chronic diseases (often called psychosomatic diseases) are caused by the homeostatic imbalance in one or more components of the hypothalamic–pituitary axis and/or psychoneuroimmunological factors. These studies emphasise the similarities between the immune and endocrine systems and hormone/cytokine interactions as well as differences in endocrine–immune responses to acute and chronic psychosocial stress.

Further research, examining the role of cytokine involvement in acquired glucocorticoid resistance in illnesses like depression, has expanded our understanding of the complexity of the endocrine–immune response to psychosocial stress. There is consistent correlation between stress, environmental factors and poor lifestyle with development of metabolic disorders and other diseases.

Psychosocial Stress

Many studies have demonstrated that physiological or psychological stress is a major contributing factor to ill health, particularly for CMDs. While it is difficult to objectively devise a standard measure of stress, several psychosocial factors including anxiety, depression, work stress and family stress correlate with low HRV. Psychosocial stress also correlates with a higher risk of CVDs and arrhythmias. Studies below have demonstrated how higher stress (a major risk factor for T2D and its complications) correlates with lower HRV.

In a clinical study among 52 healthy individuals, psychosocial stress was recorded in a diary at 1 hour interval showing that excess of worries was associated with lower HRV recorded with Holter ECG. The findings revealed that psychosocial risk factors were significantly associated with increase in heart rate and lower HRV during waking, as well during sleeping. Mental stress may be characterised with excess of thinking; frequency and duration, aggression, agitation, feeling of hopelessness and weeping sighing behaviour as well as duration, time and quality. It is known that low HRV may be associated with cardiovascular, endocrine and immune imbalance biomarkers compared to those participants with high HRV. It has been also observed that reduced resting HRV may be associated with lower vagal tone (using mental stress test on healthy individuals) and indicated that lower HRV group (compared to high HRV group) showed impaired recovery of diastolic blood pressure, cortisol and tumor necrosis factor-alpha. To summarise, psychosocial stress is one of the major risk factors for MetS and T2D, and it is marked by reduced HRV parameters. It is important to add that relaxation, slow breathing or any stress reduction intervention increases the HRV.

Lifestyle Factors

Lifestyle factors (physical inactivity, unhealthy diet, alcohol, insomnia, etc.) are major risk factors for pathophysiology changes (e.g., chronic inflammation, MetS) in any chronic disease. Evidence has shown that most of these lifestyle choices (that drive pathophysiology towards chronic disease) contribute to reduced HRV.

- Available evidence strongly suggests that T2D is an inflammatory disease and inflammation is a primary cause of obesity-linked insulin resistance, hyperglycaemia and hyperlipidaemia, rather than merely a consequence. Correlation studies between circadian markers and HRV are also well documented since many HRV parameters (high
Heart rate variability (Y-axis = standard deviation of
...
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50–60 Hz) are not conclusive of this insight to identify energy expenditure, autonomic advances in technology and analytics may enable integration to summarise, it is possible that the key environmental drivers of autonomic cardiovascular control may be observed in patients with insomnia, who show a shift of the sympathovagal balance towards predominance of sympathetic modulation both during day and night.[33]

• Physical inactivity and low resting HRV were associated with increased coronary heart disease incidence in the Whitehall II study, after adjustment for smoking and high alcohol intake.[34]

• Similarly, dysregulation of hypothalamic–pituitary–adrenal axis was observed in a study of apparently health 543 men with top tertile of the self-reported individuals showing higher cortisol levels and lower HRV compared to men in the lower two tertiles of alcohol consumption. The inverse relationship between cortisol and HRV was greatly attenuated in the heavy drinking group even after accounting for a number of potential confounding factors.[35]

It is possible that increased intake of unhealthy diet, mental stress, sedentary lifestyle, tobacco and alcoholism may be associated with neurohormonal dysfunction that may cause decline in HRV.[36]

Environmental Factors

Apart from mental stress, external environmental factors, radiations, pollutants, electromagnetic fields, working time, fatigue etc., may influence neurophysiology and the reduced HRV. A recent systematic review pointed out a detailed list of work-related factors that can influence HRV.[37] Night shift work and other factors that disturb sleep can also have adverse effects on HRV. However, the results of the impact of electromagnetic field on HRV (most of the work related to the effects of electric and magnetic fields exposure is in the area of electrical frequencies of 50–60 Hz) are not conclusive and further work is needed to form a specific conclusion.[38–40]

Similarly, geomagnetic solar and cosmic ray activities can also influence cardiovascular health, however, the evidence is limited to draw definite conclusion.[41] A recent study has suggested that daily ANS activity not only responds to changes in solar and geomagnetic activity but also is synchronised with the time-varying magnetic fields associated with geomagnetic field-line resonances and Schumann resonances. The study found that the participants’ HRV rhythms synchronised across the 31-day period at a period of approximately 2.5 days, even though all 10 participants were in separate locations.[42]

To summarise, it is possible that the key environmental drivers of autonomic imbalance correlate with reduced HRV. Further advances in technology and analytics may enable integration of this insight to identify energy expenditure, autonomic imbalance, stress and its effect on the physiology and metabolism.[43] A meaningful example to understand how energy expenditure, oxygen consumption, accelerometer (movement) and HRV data can be leveraged using modern technology is covered in this White Paper.[44]

Autonomic Imbalance, Metabolic Syndrome and Heart Rate Variability

Autonomic imbalance and MetS are critical indicators of chronic disease, specifically CVD and T2D. The review of research provides sufficient evidence on the correlation between autonomic imbalance and metabolic disorders. The common factor in both these conditions is some form of ‘reduced’ HRV parameters.

Contribution of autonomic imbalance to the development of MetS is well documented.[45] However, the ability to identify the impact is often invasive and HRV could provide a ‘useful, non-invasive’ marker in such situations. Many studies have correlated reduced HRV with one or many components of MetS. The Framingham Heart Study revealed that lower HRV (time domain measures), increased age, cigarette smoking and being male significantly increased the odds of developing MetS within 12 years of follow-up.[46] Specifically, a ‘one standard deviation of decrease’ in SDNN (a time domain parameter of HRV) increased the odds of developing MetS by 43%. A clinical study among 1933 patients, aged 18–65 years, showed that increased sympathetic activity predicts an increase in metabolic abnormalities over time.[47]

These findings suggest that a deregulation of the ANS is an important predictor of CVDs and diabetes through lipid metabolism and blood pressure. Jarczok et al. found a significant negative correlation between HRV and glycemic status in a sample of 2441 healthy workers, after adjusting for MetS components.[48] Liao et al. reported an association between low HRV and multiple metabolic disorders (MMS), namely, hypertension (HP), dyslipidaemia and T2D in a study involving 15,800 individuals who participated in the baseline examination of the Atherosclerosis Risk in Communities
The findings suggest that MMS disorders adversely affect cardiac autonomic control and a reduced cardiac autonomic control may contribute to the increased risk of subsequent cardiovascular events in individuals who exhibit MMS disorders (refer to Figure 2 for summary of the key outcome from that study). A study of 50 patients with MetS and 50 healthy non-MetS individuals demonstrated that autonomic function in MetS was impaired using a combination with HRT (heart rate turbulence) and HRV measures.

The evidence also suggests that reduced HRV correlates with many other parameters of the journey into the T2D continuum. For example, decreased HRV is associated with higher levels of inflammation (C-reactive protein and interleukin-6). It is possible to use HRV measures to identify autonomic dysfunction and/or MetS.

**‘Type 2 Diabetes Mellitus’ and Heart Rate Variability**

Research has demonstrated the correlation between reduced HRV and T2D disease progression [Refer to Table 1 for details]. The HRV parameters, in general, reduce as the patients move on the continuum that covers (a) diabetes risk, (b) insulin resistance, (c) diabetes and (d) diabetes complications (e.g., neuropathy).

For example, in patients with increased FINNISH risk for diabetes, the HRV was reduced as compared to healthy controls and the reduction continued as the diabetes risk increased. The studies also indicate that both time and frequency domain parameters are lower in diabetes patients compared to controls and the HRV reduces further when we consider the patients with chronic complications compared to just diabetes. The reduced HRV parameters indicate impaired parasympathetic and sympathetic activity (with or without clinical signs of diabetes autonomic neuropathy). With better understanding of specific parameters, measurement methodology and technology enhancements, HRV could be leveraged as an important marker to indicate not only diabetes risk but also possible risk of diabetes complications especially CAN.

To summarise, the journey in T2D continuum requires the identification of simple but clinically significant non-invasive marker such as HRV that remains consistent and clinically significant across the continuum. It is possible that HRV may be a useful marker, since it is a significant indicator of the imbalance caused by stress, ANS and chronic disease. Moreover, as we move towards T2D in the continuum, the studies have also demonstrated impaired HRV all the way from stress to T2D. Having established the correlation between HRV and the risk factors eventually contributing to T2D, it would be prudent to identify and explore what happens in case of a T2D complication.

**Diabetes Complications and Heart Rate Variability**

The review focuses on cardiac complications and T2D, specifically coronary artery disease (CAD), myocardial infarction (MI) and CAN. HRV decreases further with the complications of T2D and could be a meaningful predictor of autonomic dysfunction, neuropathy and morbidity/mortality risk-related MI. CVD and HRV are being studied aggressively since the last two decades and more research and clinical insights are likely to enhance the role of specific HRV parameters in this area. Table 2 highlights some of the studies demonstrating the evidence about HRV and diabetes complications with highlights captured below:

- CAN represents a significant cause of morbidity and mortality due to high risk of cardiac, arrhythmia and

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**Table 1: Summary of a few representative studies correlating T2D and heart rate variability**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects</th>
<th>HRV parameters, durations</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>[52]</td>
<td>1899</td>
<td>5 min time, frequency domain analysis</td>
<td>Reduced HRV was associated with insulin resistance and lower insulin sensitivity. Decreased ISI was linked with parasympathetic dysfunction, primarily in non-overweight individuals</td>
</tr>
<tr>
<td>[53]</td>
<td>1999</td>
<td>2 h (ambulatory reading), time, frequency domain analysis</td>
<td>The presence of reduced HRV in subjects with T2D suggests the presence of heightened sympathetic activity and/or reduced vagal activity</td>
</tr>
<tr>
<td>[54]</td>
<td>130 (4 risk profiles)</td>
<td>5 min, RR interval, linear and non-linear analysis</td>
<td>The individuals at high risk T2D have lower heart rate variability</td>
</tr>
<tr>
<td>[55]</td>
<td>69 without T2D</td>
<td>24 h, time and frequency domain analysis</td>
<td>The obtained results suggest that even slightly elevated risk for developing diabetes mellitus may be related to impaired HRV</td>
</tr>
<tr>
<td>[56]</td>
<td>400 (200 control, 200 T2D)</td>
<td>5 min frequency domain</td>
<td>a. HRV parameters were reduced in T2D and parameters depicting parasympathetic modulation were more reduced (compared to sympathetic modulation)</td>
</tr>
<tr>
<td>[49]</td>
<td>2359</td>
<td>2 min time and frequency domain</td>
<td>HRV indices were significantly lower in individuals with multiple metabolic disorders indicating reduced cardiac autonomic control. This may contribute to the increased risk of subsequent cardiovascular events in these individuals</td>
</tr>
</tbody>
</table>

ISI: Insulin Sensitivity Index, HRV: Heart rate variability, HbA1c: Hemoglobin A1c, RR: Time interval between consecutive heart beats measured in echocardiogram
Impaired HRV is a strong, independent predictor of increased mortality after acute MI. Combination of MI and T2D has more significant negative effect on HRV with increased the morbidity and mortality risk

- For CAN, HRV is emerging as a measure that can identify the mortality and comorbidity, especially for T2D patient.

It is clear that HRV is a sensitive cardiac indicator, which may help to predict the cardiac morbidity and mortality among T2D patients. HRV may be useful in the early diagnosis and treatment of complications among patients with diabetes mellitus. Therefore, it is possible that reduced HRV is a marker of autonomic imbalance or metabolic disorder and also a meaningful marker for predicting and managing T2DM.

### Clinical Significance of Heart Rate Variability

There are many possibilities for clinicians to leverage the insights from HRV data. First, HRV can indicate early subclinical manifestation of autonomic dysfunction, and this could be of value from clinical perspective to understand the risk associated with the subject and further management. In other words, having HRV insight may influence the aggressiveness of the intervention and the choice of therapy when dealing with hyperglycaemia and the complications and also for identifying potential risks, which are not obvious (e.g., CAN). Second, the management of T2D needs

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**Table 2: Summary of a few representative studies summarizing heart rate variability in cardiac complications and T2D**

<table>
<thead>
<tr>
<th>Ref</th>
<th>T2D complication</th>
<th>Subjects</th>
<th>HRV parameters, durations</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>[57]</td>
<td>CAN</td>
<td>Review of 8 studies</td>
<td>Full range of parameters across the studies</td>
<td>HRV is useful to discriminate cardiac autonomic neuropathy in person with diabetes. Review also identified specific parameters of HRV having better discriminatory power to detect autonomic dysfunction with high sensitivity and specificity</td>
</tr>
<tr>
<td>[58]</td>
<td>CAN</td>
<td>50 children</td>
<td>Time and frequency domain</td>
<td>HRV analysis can detect early subclinical alterations of the autonomic nervous system in asymptomatic patients with insulin dependent T2D, which seem to consist mainly in a parasympathetic impairment</td>
</tr>
<tr>
<td>[59]</td>
<td>CAN</td>
<td>189 health control and 93 T2D</td>
<td>Supine short duration time, Frequency and non-linear measures</td>
<td>The most significant decrease in HRV related to diabetes and thus presence of autonomic neuropathy was observed within the first 5-10 years of disease progression</td>
</tr>
<tr>
<td>[60]</td>
<td>CAN</td>
<td>57 T2D and 54 non-diabetic</td>
<td>Short duration time and frequency domain measures</td>
<td>The study identified that early detection of cardiac autonomic neuropathy can help us detect the development of atherosclerosis earlier in T2DM to prevent unfavorable outcomes. Study found an inverse association between total power of HRV and median HbA1c levels (i.e., high HbA1c meant lower total power) indicating that parasympathetic neuropathy was present since early stage T2D</td>
</tr>
<tr>
<td>[61]</td>
<td>MI</td>
<td>Review of 21 articles (&gt;3400 subjects)</td>
<td>Various measures</td>
<td>Disrupted HRV (low SDNN) is associated with higher adverse outcome and there is a direct relationship between SDNN and mortality after MI (while noting that each patient’s SDNN needs careful evaluation)</td>
</tr>
<tr>
<td>[62]</td>
<td>MI</td>
<td>50 healthy volunteers with 50 MI subjects</td>
<td>24 h HRV</td>
<td>HRV measurement becomes a useful clinical indicator for T2D with MI related complications. Specifically, the study concluded that HRV decreased in subjects with MI and got worse in diabetic patients with myocardial infarction</td>
</tr>
<tr>
<td>[63]</td>
<td>CAD</td>
<td>54</td>
<td>24 h HRV</td>
<td>The measures of HRV are associated with angiographic coronary artery disease (CAD) in patients with stable angina, independent of traditional risk factors, comorbidity, medication, and Framingham risk. In addition, in patients with high risk of CAD, HRV were even more predictive. Measures of HRV may provide specific advantages in clinical practice to improve the risk reclassification of angiographic CAD</td>
</tr>
<tr>
<td>[64]</td>
<td>CVD</td>
<td>Review</td>
<td>Various recordings</td>
<td>The study concluded that lower HRV is associated with 32%-45% increased risk of a first cardiovascular event in a population without known CVD risk. This indicates that lower HRV could add high mortality risk and morbidity for existing T2D subjects</td>
</tr>
<tr>
<td>[65]</td>
<td>Coronary heart disease risk and T2D</td>
<td>11,654, 8 years of follow-up</td>
<td>Supine 2 min time and frequency domain</td>
<td>At the population level, a lower HRV (reflective of impaired cardiac autonomic control) is statistically significantly related to the development of CHD among individuals with diabetes, independent of markers of the duration/severity of the glucose metabolism impairment. The data suggest a contribution of an impaired cardiac autonomic control to the risk of CHD among individuals with diabetes</td>
</tr>
</tbody>
</table>

HRV: Heart rate variability, HbA1c: Hemoglobin A1c, CHD: Coronary heart disease, CVD: Cardiovascular disease, CAD: Coronary artery disease

sudden death, possibly related to silent myocardial ischemia. Decrease in HRV is the earliest clinical indicator of CAN. Regular HRV testing provides early detection and thereby promotes timely diagnostic and therapeutic interventions for diabetic neuropathy.

- Impaired HRV is a strong, independent predictor of increased mortality after acute MI. Combination of MI and T2D has more significant negative effect on HRV with increased the morbidity and mortality risk
- For CAN, HRV is emerging as a measure that can identify the mortality and comorbidity, especially for T2D patient.
to be inclusive and must incorporate preventive intervention. Therefore, the work must begin before the manifestation of T2D (i.e., prevention must focus on the risk factors, autonomic imbalance and MetS). The interventions must integrate complementary therapy interventions along with medical treatment during the disease stage and the complications. Third, better understanding of interventions that could improve HRV may enable clinicians to guide the patient towards lifestyle that could enhance HRV and hence the quality of life (and could slow down the disease progression).

It is possible to develop a holistic plan— that includes the patient at the centre of the treatment plan, with the use of non-invasive marker such as HRV. This can enhance the understanding of existing risk factors (e.g., insomnia or psychosocial stress) to make an intervention plan that can empower both the clinician and the patient to make more meaningful interventions on the basis of risk factors as well as pathophysiology for the lifestyle choices and the medical treatment.

**Conclusion**

The HRV displays beat-to-beat variation resulting in changes in ANS activity and HRV negatively correlates with stress. The review of clinical studies measuring HRV parameters in patients experiencing stress, autonomic dysfunction, CVD, T2D and diabetes complications consistently reveals the impairment of HRV parameters along the diabetes continuum (from homeostasis to stress, autonomic dysfunction, MetS, insulin resistance, T2D and T2D complications). From clinical perspective, it is possible to leverage HRV to understand the risk factors and integrate that knowledge into the treatment plan. Experimental studies and clinical evidence indicate that increased intake of unhealthy diet, mental stress, sedentary lifestyle; tobacco intake, sleep disruption and alcoholism may be associated with neurohormonal dysfunction, which may cause decline in HRV.

Further studies revealed that majority of the chronic diseases such as diabetes, HP, heart attack, neuropsychiatric diseases and cancer are associated with decreased HRV.

Simple methods are needed to measure HRV that may be useful in the early diagnosis of neurohormonal dysfunction, which may be important for early management. Beyond the identification of the clinical problems, there is an opportunity to apply patient-centric interventions to improve HRV, thereby enhancing the autonomic function and improve the quality of life. Further studies in this area should not only be limited to the clinical importance of HRV measures for diabetes management but also on the interventions to improve HRV regardless of where the individual is in (or outside) the diabetes continuum.

**Limitations**

While HRV provides meaningful insights, additional work in this area will improve our understanding and engage individuals as well as medical community in this effort. Specifically, the future work should include (a) identifying which HRV parameters are more meaningful at each stage and also throughout the continuum, (b) documenting which specific measures (e.g., power or ratio) should be used during each stage of the continuum, (c) identifying a ‘meaningful range’ for each parameter to make the measure more useful across the continuum, (d) identifying the duration (24 h Holter or 5 min fixed time during the day) and the method (e.g., supine) of the measure and (e) what additional data could provide meaningful insights when used along with HRV at each stage of the illness continuum. As we standardise the measures and get more insights based on quantity and quality research, HRV holds significant promise for the entire continuum.

**Future Implications**

The advances in technology and analytics are likely to make it easier and more actionable not only for clinical use but also at the individual level to measure HRV parameters.[70] The HRV trend (i.e., reduction) across the illness continuum can be a useful indicator of the balance between illness and wellness at an individual level as well. From the clinical perspective, HRV holds promise not only in predicting the disease (through stress and ANS-related imbalance) but also in measuring and addressing the disease progression.

There is also an opportunity to integrate HRV with other non-invasive (breathing rate, movement i.e., energy expenditure, galvanic skin response and VO2 consumption) and invasive methods; circadian rhythm of key hormones and catecholamines to further enhance the understanding of the metabolism and stress resilience of the individual at different stages of the continuum. There are commercially available devices for use at both individual wellness and professional sports level that have started doing some of this combination which needs validation and further studies by concerned experts.[71] Further work in the area of improving HRV parameters (and thereby enhancing the ANS function) over a sustained duration could be of clinical importance for an integrated approach to managing the chronic disease such as T2D.

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**Conflicts of interest**

There are no conflicts of interest.

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