Chapter 15
Diabetes

Introduction

Diabetes mellitus (DM) comprises a group of common metabolic disorders sharing the phenotype of hyperglycemia. Several subtypes are described and today much is known about the causes. In complex interaction, genetics, environmental, social, and lifestyle factors contribute to a phenomenon that more and more often is being called a diabetic epidemic. Depending on the etiology of DM, factors involved may include reduced insulin secretion, decreased glucose usage of the body, and increased glucose production. DM causes a plethora of pathophysiological changes in multiple organ systems that impose a tremendous burden on individuals and health systems. In the US, DM is the leading cause of end-stage renal disease, lower extremity amputations, and adult blindness.

Up to 50 % of patients with diabetes develop diabetic neuropathy. NIDDM patients have an increased likelihood to develop mononeuropathy and other forms (Boulton et al. 2004). Diabetic autonomic neuropathy causes substantial morbidity and increased mortality, particularly if cardiovascular autonomic neuropathy (CAN) is present (Boulton et al. 2005). The effects of DM on cardiac health are so profound that some cardiologists have termed DM as a cardiac disease with at the same time elevated blood glucose levels.

Diabetic autonomic neuropathy (DAN) is a common consequence of diabetes. It is related to an increased risk of cardiovascular mortality and associated with multiple symptoms and impairments. Various prevalences have been reported, in part because of the methods of assessment. In cohorts of asymptomatic individuals with diabetes, approximately 20 % had abnormal cardiovascular autonomic function already in early illness. DAN frequently coexists with other peripheral neuropathies and other diabetic complications, but DAN is frequently isolated, preceding the detection of other complications.

Major clinical manifestations of DAN include resting tachycardia, exercise intolerance, orthostatic hypotension, changed sudomotor dysfunction, constipation, gastroparesis, impaired neurovascular function, hypoglycemic autonomic failure,

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and erectile dysfunction. GI disturbances are common, and any section of the GI tract may be affected. Gastroparesis should always be suspected in individuals with erratic glucose control. A radiographic gastric emptying study can definitively establish the diagnosis of gastroparesis; a reasonable approach can also be use to conduct ultrasound exams (Kashyap and Farrugia 2010). Constipation is the most common lower GI symptom but can alternate with episodes of diarrhea and DAN can mimic irritable bowel syndrome. Diagnostic approaches should assess autonomic function and rule out neoplasia. Disruption of microvascular skin blood flow and sudomotor function may be among the earliest manifestations of DAN and lead to dry skin, loss of sweating, and the development of fissures and cracks that allow microorganisms to enter. These changes ultimately contribute to the development of ulcers, gangrene, and limb loss. Cardiovascular autonomic neuropathy (CAN) is the most studied and clinically important form of DAN usually characterized by heart rate variability. DAN is associated with an increased risk of silent myocardial ischemia and mortality. Proceedings from a consensus conference in 1992 recommended that three tests (RR variation, Valsalva maneuver, and postural blood pressure testing) or longitudinal testing of the cardiovascular autonomic system be conducted in diabetic patients (Vinik et al. 2003).

Early detection of DAN in a diabetic patient is of paramount importance since it can cause prompt therapeutic interventions with a significant survival benefit (Karayannis et al. 2012). Measurement of HRV at the time of diagnosis of type 2 diabetes and within 5 years after diagnosis of type 1 diabetes (unless an individual has symptoms suggestive of autonomic dysfunction earlier) serves to establish a baseline, with which 1-year interval tests can be compared. Regular HRV testing provides early detection and makes early diagnostic and therapeutic interventions possible. Interventions include improving metabolic control and using therapies such as ACE inhibitors and beta-blockers are proven to be effective for patients with CAN (Vinik et al. 2003).

In diabetic autonomic neuropathy several test batteries are used. Minimal examination procedures should include (1) heart rate response during deep breathing (six times per minute), (2) Valsalva maneuver, and (3) postural blood pressure testing. (1) Heart rate response during deep breathing can be used without or with HRV algorithms.[1] It is possible to use either 24 h Holter ECG or 7 min HRV measures if frequency-domain measures are used (Vinik et al. 2003). The first point (paced breathing) has been challenged. Most probably, usual HRV procedures with spontaneous breathing are sufficient (Denver et al. 2007; Wittling and Wittling 2012). Normative values have been proposed (Ziegler et al. 1992; Risk et al. 2001) and HRV is mentioned as one of three standard techniques besides autonomic innervation imaging techniques, microneurography, and baroreflex analysis for detecting DAN (Karayannis et al. 2012).

[1] Note that paced respiration has rather historical reasons related to early studies and to make newer data comparable with them. For a more extended discussion see Chap. 4.

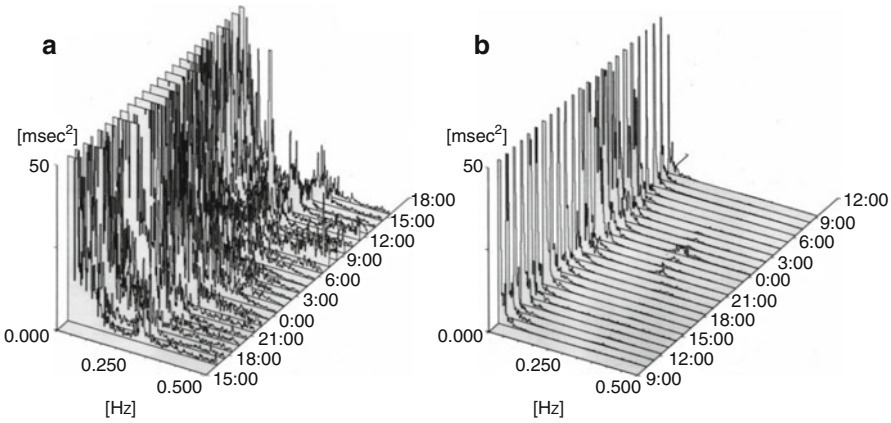

Fig. 15.1 Two typical examples for power spectra during 24 h. (**a**) A 56-year-old man without diabetes. (**b**) A 64-year-old female with diabetes (Nishimura et al. (2004), with permission of Oxford University Press)

HRV and Diabetes

Because of the early recognition of the association of HRV and autonomous dysfunction, diabetes is one of the most established areas in which clinical studies include HRV measurements. The Diabetes Control and Complications Trial Research Group (1988, 1993) conducted a major study looking at the effect of better diabetes treatment on different measures of outcome using HRV among others. They followed changes in autonomic tone by a paced-breathing approach. HRV as a measure of CAN remained significantly higher in the former intensive treated group compared with the former conventional group (Pop-Busui et al. 2009). Marked abnormalities in heart rate variability were significantly associated with and predictive of progressive renal deterioration at 1 year in diabetic patients. Heart rate variability was a significant and independent predictor of abnormalities in creatinine clearance in this small study (Burger et al. 2002).

In a study with 217 nondiabetic and diabetic dialysis patients with and without left ventricle hypertrophy, 24 h HRV was obtained. Mean pNN50 and SDANN, TP, LF, and HF were lower in diabetic than in nondiabetic patients, but LF/HF ratio did not differ. In diabetic patients LVMI correlated negatively with pNN50 ($r=-0.270$) and HF ($r=-0.277$). In nondiabetic patients LVMI did not correlate with any HRV variables (Nishimura et al. 2004) (Fig. 15.1).

In a longitudinal epidemiological study on a population-based cohort of 6,245 individuals, a 2-min HRV measure was taken in the beginning and a 6 min recording after 9 years. Due to the short-term recording, only SDNN and rMSSD were calculated. Diabetic subjects had lower SDNN and rMSSD than healthy participants. Diabetic persons had a greater decrease in SDNN and rMSSD by factors of 1.4 and 1.9 (Schroeder et al. 2005) (Fig. 15.2).

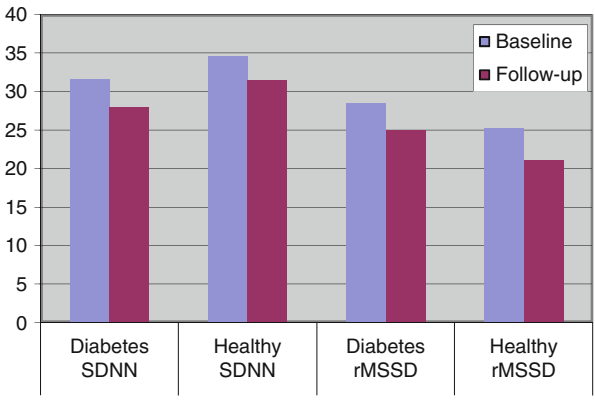

Fig. 15.2 Changes in SDNN and rMSSD in $n = 3{,}567$ healthy persons and $n = 457$ persons with diabetes (Adapted with data from Schroeder et al. (2005))

In a study, 30 patients with painless and painful DN were followed over 2 years and examined with help of HRV, electrophysiological measures, and qualitative sensory testing (QST). Vibration thresholds deteriorated over time and c-fiber function correlated with pain intensity, but there was no correlation between HRV values and painful DN (Krämer et al. 2004). Reduced heart rate variability (HRV) has been also related to diabetic sensorimotor polyneuropathy. Eighty-nine diabetic subjects and 60 healthy volunteers were assessed: SDNN had an inverse relationship with ordinal categories of increasing DSP severity. Despite statistical significance, there was substantial overlap of SDNN between diabetic patients and the healthy volunteers. Higher glycated hemoglobin A(1c) and systolic blood pressure, and measures of large and small fiber neuropathy, were independently associated with lower SDNN. In some control subjects without polyneuropathy, HRV was also low (Orlov et al. 2012).

In a population-based survey, 1,030 males and 957 females were assessed for cardiovascular risk factors like diabetes, hypertension, obesity, dyslipidemia, smoking, and low physical activity. In men, after adjustment for alcohol intake and age, independent determinant for low SDNN were diabetes, obesity, and smoking; in women only diabetes. The authors conclude that diabetes is the primary determinant of reduced HRV in the general population (Ziegler et al. 2006).

In a diabetes prevention program, early treatment options were tested on adults who were at high risk for developing diabetes (i.e., BMI $\geq$24 kg/m^2, fasting glucose 5.3–6.9 mmol/l, and 2-h glucose 7.8–11.0 mmol/l). The 2,980 participants were randomized to three different groups: (1) standard lifestyle recommendations plus placebo twice daily, (2) standard lifestyle recommendations plus 850 mg of metformin twice daily, and (3) an intensive program of lifestyle modification and followed up for 3, 2 years, with annual examinations. HRV measures were based on 10-s digital rhythm strips; SDNN and RMSSD were calculated. The lifestyle group showed lower basal heart rate and higher HRV with metformin and placebo arms. Increasing SDNN and rMSSD during the study were associated with lower diabetes risk in the lifestyle arm (Carnethon 2006).

A study showed a relationship between subjects with different degrees of insulin resistance and HRV alterations. In detail, SDNN showed significant reduction in all tested groups compared with a healthy control group. At night LF nu was higher in all patient groups. Patients with several other potentially confounding factors had been excluded. Interestingly, the insulin-resistant subjects with not yet impaired glucose regulation showed reduced SDNN values already. The subjects with type 2 diabetes mellitus had greater autonomic dysfunction than the insulin-resistant subjects in the other groups (Perciaccante et al. 2006). In a mixed group ($n = 34$) with peripheral neuropathy due to diabetes, alcoholism, paraneoplasia, and lack of B12, HRV in rest (RMSSD), associated with Valsalva maneuver and posture, was reduced compared to 190 non-matched healthy controls (Haegele-Link et al. 2008).

Heart rate variability correlates with lung diffusion capacity for carbon monoxide (DLCO), a general measure for lung diffusion capacity in diabetes patients without clinical pulmonary abnormalities. The autonomic function was assessed by Holter monitoring. Strongest correlations were found with SDNN and LF. The authors debate a possible influence of a disturbed autonomic function on lung diffusion capacity in early diabetes (Pitocco et al. 2008).

Metabolic syndrome in younger adults is associated with lower LF, Hf, and TP in short-term HRV. In men, waist circumference was the strongest individual metabolic syndrome component associated with HRV ($n = 1{,}889$ subjects between 24 and 39) (Koskinen et al. 2009).

Five-minute HRV was inversely correlated with IL-6 in 30 male patients with metabolic syndrome compared with 153 controls (Brunner et al. 2002). Patients with impaired glucose tolerance had increased TNF alpha, TNF alpha receptor II, and IL-6, but there were no correlations between HRV and inflammatory parameters (Diakakis et al. 2005). Looking further at these interactions, nondiabetic controls, newly diagnosed, and established diabetic patients were included in a study of inflammatory parameters and short-term HRV. As expected, heart rate variability was reduced in all diabetics. Interleukin-6 was higher in diabetics, as was the high-molecular-weight adiponectin to leptin ratio. Interleukin-6 correlated negatively with HRV. Ratios of adiponectin to leptin correlated positively with measures of autonomic balance (Lieb et al. 2012). This study confirmed and extended results observed in an earlier study where IL-6 correlated with HRV changes in paced-breathing investigations (González-Clemente et al. 2007).

In a study including 57 diabetic and 54 nondiabetic subjects free of coronary heart disease, significant reduction HF nu and TP was demonstrated in diabetic participants. An inverse association between total power and median HbA (1c) was observed (Fakhrzadeh et al. 2012).

In a study of the relationships between HRV and several measures of arterial stiffness in youth with ($n = 344$) and without ($n = 171$) type 1 diabetes, an association between low SDNN and peripheral arterial stiffness was demonstrated. The association remained statistical significant also after adjustment for CAD risk factors (Jaiswal et al. 2013b).

Role of HRV in Evaluation of Diabetic Patients

HRV changes might not only predict cardiac events and mortality, but also progression of carotid atherosclerosis. Studies were carried out 5–6 years after diagnosis (baseline) and repeated 8 years after diagnosis (follow-up). At baseline, patients had decreased LF. Reduced common carotid artery diameter and atherosclerotic intima-media thickness (IMT) both correlated with HRV at baseline. At follow-up, all HRV variables decreased significantly. Furthermore, patients with lower LF power at baseline had a larger increase in the thickness of the carotid bulb intima-media at follow-up (Gottsäter et al. 2006). This is in accordance with the already mentioned study of the Diabetes Control and Complications Trial Research Group (Pop-Busui et al. 2009).

The importance of Holter monitoring has been challenged in a study with a follow-up of 15 years where only LF was an independent risk factor for all-cause mortality, but Valsalva test, heart rate response to standing (30:15 ratio), and handgrip test had a higher predictive value (May and Arildsen 2012). HRV decreases depending on the number of risk factors (Hsiao et al. 2011).

Early Detection of DAN: Desirable or Not Necessary?

Diabetic autonomic neuropathy (DAN) is associated with increased morbidity and mortality and can have an incidence of 23.4 per 1,000 person years in diabetic patients (Witte et al. 2005). As described, several data confirm early HRV changes in different diabetic patients.

Already young diabetic patients around 18 with a mean duration of illness of 9 years have obvious changes in HRV (Jaiswal et al. 2013a). This has been shown in different studies, e.g., in one looking at participants with increased fasting blood sugar showing significantly changed HRV parameters (Thiyagarajan et al. 2012). However, a closer look at the results reveals rather subtle differences. SDNN for instance is 30.94 ± 11.92 in participants with impaired glucose metabolism compared with 37.82 ± 15.61, LF/HF 1.98 ± 1.92 compared with 1.18 ± 1.07. This makes it difficult to identify relevant changes in individual patients.

Vinik writes “Screening for autonomic dysfunction should be performed at the diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes, particularly in patients at greater risk due to a history of poor glycemic control, cardiovascular risk factors, and macro- or microangiopathic diabetic complications” (2012). But are there data showing that early testing of HRV in diabetes patients is beneficial?

Whether early diabetes testing has effects on the development of DAN is still controversial. A recent Danish study was not able to show differences in DAN development in an intensively treated group of patients compared with standard treatment (Charles et al. 2013).

Concluding Remarks

Today there is overwhelming statistical evidence that already early in the course of diabetes different HRV parameters are reduced. During the disease HRV diminishes further, together with changes in other clinical parameters discussed extensively by Vinik (2012). Several diabetologists regard HRV as a standard examination tool and recommend it highly for baseline examinations and follow-up patients. There is limited evidence that interventions can delay further fall of HRV, in some cases even cause an increase, which is considered (but not proven) as a surrogate of better health in this patient group. Considering this, it is surprising that HRV is not more often used in diabetologic outpatient departments.

In contrast to other clinical areas, nonlinear indices are not used very often in the evaluation of diabetic patients (with exceptions such as Khandoker et al. (2009)). This is most probably because HRV seems to be "established" in this area. However, it is desirable to include some of the more often used nonlinear parameters in further studies.

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