

Baroreceptor sensitivity and diabetes mellitus

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Abstract

Diabetes mellitus (DM) is a disease of increasing incidence and prevalence. Arterial baroreceptors are stretch-sensitive receptors, which in a reflex manner are involved in the homeostatic control of arterial blood pressure. Diabetic subjects have depressed baroreflex sensitivity (BRS), although the exact pathomechanisms are unclear. In this review, we discuss the features, clinical and prognostic implications of reduced BRS for diabetic patients and the potential involvement of cardiovascular autonomic neuropathy and atherosclerosis. Finally, we demonstrate evidence on interventions (e.g. pioglitazone, alpha-lipoic acid, leptin, fluvastatin, physical training etc.) which could improve BRS and ameliorate cardiovascular autonomic dysfunction in diabetic patients. (Cardiol J 2013; 20, 5: 453–463)

Key words: arterial baroreceptors, autonomic dysfunction, baroreflex sensitivity, cardiovascular autonomic neuropathy, diabetes mellitus

Introduction

Diabetes mellitus (DM) is a metabolic disease with increasing incidence and prevalence. In DM, there is an alteration in the cardiovascular reflex response and one of the key elements of this alteration is the impaired response from arterial baroreceptors. The deterioration in the baroreflex function in diabetic patients, its features, clinical and prognostic consequences and the potential for its reversal are discussed in this article.

However, the following important keywords need to be defined in order to afford the reader a better understanding of the concepts presented in this article.

Baroreflex sensitivity (BRS). An autonomic assessment parameter which provides insight on the autonomic regulation of cardiovascular function. BRS measures the reflex-mediated change in R-R interval produced by a change in the systolic blood pressure (BP).

Autonomic dysfunction. A malfunction or disease of the autonomic nervous system. DM is a common cause of autonomic dysfunction. Impaired BRS is indicative of autonomic dysfunction.

Cardiovascular autonomic neuropathy (CAN). A form of diabetic autonomic neuropathy (DAN) characterized by cardiovascular autonomic dysfunction resulting from damage to the autonomic nerve fibers innervating the heart and blood vessels. Impaired BRS is an element of CAN.

Physiology of arterial baroreceptors

The reflex response from baroreceptors (baroreflex) is one of the body's mechanisms for the homeostatic control of arterial BP and the maintenance of the optimal perfusion of critical organs such as the brain, heart, etc. Arterial baroreceptors are stretch-sensitive receptors found in the arterial walls (localized mainly in the carotid sinus of the carotid arteries and in the walls of the aortic arch) [1].

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Arterial baroreceptors are innervated and remain under the reflex neural control. Afferent fibers from the carotid and aortic baroreceptors pass via the glossopharyngeal and the vagal nerves into the nucleus tractus solitarius in the medullary area of the brainstem [1, 2]. The efferent fibers pass via the parasympathetic and sympathetic arms of the autonomic nervous system to the heart and blood vessels [2], as the baroreceptor reflex consists of two main components namely the cardiac and the vascular components [2, 3]. The baroreflex system for the control of arterial pressure is based on a negative feedback mechanism and is the most rapid of all the body's BP control mechanisms [1].

An increase in systolic BP (SBP) stretches the arterial baroreceptors and they respond by increasing their rate of action potential generation which is then transmitted to the brain stem. Appropriate compensatory responses are initiated by the cardiovascular control center in the brainstem in order to decrease SBP. This is achieved via an increase in the vagal (parasympathetic) outflow and a decrease in the sympathetic outflow to the heart and blood vessels. The resultant effect is a decrease in heart rate (bradycardia), cardiac contractility, stroke volume, peripheral vascular resistance and venous return [1, 4].

Methods of assessing baroreflex function in humans

The functional integrity of arterial baroreceptors can be assessed using various BRS assessments. The rationale behind the BRS testing is to see how a spontaneous or provoked (using either vasoactive drugs or certain maneuvers) change in SBP brings about a reflex-mediated change in RR intervals [4–6].

In the **vasoactive drug (pharmacological) method**, the drug that has been traditionally used for the BRS assessment is the alpha-adrenergic agonist phenylephrine, and the test is designated as a phenylephrine test (BRS-Phe). Injecting phenylephrine (a vasoconstrictor) brings about an increase in SBP, which induces a reflex-mediated change in RR intervals [4, 5, 7]. As there is a linear association between an increase in SBP and the subsequent increase in RR intervals, the BRS-Phe is expressed as a slope of the regression line linking changes in SBP and RR intervals [4, 5]. Vasodilators like sodium nitroprusside or nitroglycerin can also be used to assess BRS [4, 7]. However, the BRS-Phe remains the gold standard for BRS evaluation.

The **Valsalva maneuver** is done by either expiring against a closed glottis [4] or blowing (exhaling) continuously into a closed system for about 12 s at a pressure of at least 40 mm Hg [5]. The BRS can then be estimated from the linear regression analysis of the SBP and the RR interval changes during the phase IV of this maneuver (phase IV is characterized by BP overshoot due to the effects of prevailing vasoconstriction and the normalization of cardiac output and venous return) [4].

The **neck chamber method** involves the application of positive or negative pneumatic pressure to the neck region in order to specifically stimulate or deactivate the carotid baroreceptors in that region [3, 4]. The carotid BRS can then be obtained from the slope of the regression of the RR intervals on the neck pressure values [4].

In the **controlled breathing method (BRS-CtrBr)**, the examined subject performs regular inspirations and expirations for a certain period of time (e.g. 3–5 min) at a constant rate of e.g. 6 breaths per minute (0.1 Hz) [7, 8]. The ratio of the amplitude of RR intervals oscillations to the amplitude of SBP oscillations is another measure of BRS [7].

BRS can also be assessed using continuous recording and relating BP and RR intervals during different maneuvers that involve change in body position, e.g. **orthostasis** (where the examined subject stands upright throughout the test period [7]); the **squatting test** (here, the examined subject stands for 3 min at the beginning of the test, then squats down for 1 min, and finally stands again for another 1 min [9, 10]); and the **tilt-table method** (where both the head-up tilting and downward tilting techniques can be used [7]).

In the **microneurography method**, the slope of the relationship between muscle sympathetic nerve activity and diastolic BP is used to assess the BRS [7].

Spontaneous BRS can be obtained using the sequence and spectral analysis methods [4–6]. The **sequence method (BRS-Seq)** defines BRS as the slope of the linear regression of three or more consecutive beats (in which progressive rise/fall in SBP are accompanied by progressive lengthening/shortening of RR intervals) [4, 6]. In the **spectral analysis method**, BRS assessment is based on the relationship (in terms of gain, phase and coherence) between SBP and RR intervals in the low frequency and high frequency bands [4–6].

In healthy subjects, numerous factors influence BRS, such as: age, gender, genetic factors, baseline heart rate, baseline BP, fitness and body weight, hormone status, arterial stiffness, some drugs and physical activity [11–15].

BRS also increases in the presence of parasympathetic dominance and decreases in the presence of sympathetic dominance [5].

Diabetes mellitus, diabetic autonomic neuropathy, and baroreflex impairment

Impairment in the baroreflex function (i.e. reduced BRS) has been demonstrated in subjects with DM, both in experimental models using streptozotocin (STZ)-induced diabetic rats [16–18] and in diabetic patients [19–21]. However, some authors did not confirm such observations [22–25].

Diabetic patients quite commonly develop the so-called diabetic autonomic neuropathy (DAN). Its exact origin remains unknown, however, some authors consider this pathology as metabolic and ischemic nerve injuries due to chronic hyperglycemia [26]. Hyperglycemia-induced changes cause a decrease in endoneurial circulation (reduced blood flow to the nerves) resulting in ischemia and hypoxia [26, 27]. The attendant effect of endoneurial hypoxia is impaired axonal transport [26, 27] and finally axonal atrophy [26]. Furthermore, hyperglycemia causes an activation of the polyol pathway with the enzyme aldose reductase serving as a catalyst; this leads to the accumulation of sorbitol and fructose in the nerves thereby resulting in intracellular deficiency of myoinositol in the nerve tissues and changes in the structural nerve proteins [26, 27]. Hyperglycemia also causes oxidative stress with increased production of oxygen free radicals [26–28] which results in tissue damage [27]. In some patients, immunological and inflammatory processes can play a role in the development of neuropathy [27, 28]. Other factors leading to neuronal damage in diabetic neuropathy include decrease in nerve growth factors, and disorders in the metabolism of essential fatty acids [27, 28].

Although DAN can affect nerves innervating most body organs, its effects on the structures innervating the cardiovascular system seem to be prominent and clinically relevant [6, 27, 28]. In CAN, there occurs cardiovascular autonomic dysfunction resulting from injury to the autonomic nerve fibers innervating the cardiovascular system. The clinical manifestations of CAN [6, 27–29] include: exercise intolerance, resting tachycardia, orthostatic hypotension, silent (painless) myocar-

dial ischemia, intra-/perioperative cardiovascular lability, orthostatic tachycardia and bradycardia syndromes, increased mortality risk.

CAN seems to be associated with an increased risk for major cardiovascular events such as myocardial infarction (MI) and stroke [30–32]. Methods used in the diagnosis and evaluation of CAN include:

- heart rate variability (HRV) [6];
- the standardized (conventional) battery of autonomic function tests proposed by Ewing et al. [33] (such as heart rate [HR] response to Valsalva maneuver, HR response to deep breathing, HR response to orthostasis, BP response to orthostasis, BP response to sustained handgrip);
- spontaneous BRS [6];
- cardiac radionuclide imaging [6].

Both HRV [5, 6, 27, 28] and BRS [19, 20] are reduced in CAN patients. HRV as an assessment tool is one of the earliest indicators of CAN [5, 6, 27, 28]; its drawback however lies in the fact that its parameters are more difficult to interpret in comparison to other noninvasive autonomic tests mentioned above [5]. Cardiac radionuclide imaging as an assessment tool is not feasible for quick and routine evaluation of patients in the outpatient setting. Spontaneous BRS is one of the most promising but perhaps less-commonly-used tools for assessing cardiovascular autonomic dysfunction in diabetic patients. Comparative studies involving the use of both spontaneous BRS and conventional autonomic function tests in the diagnosis of CAN have demonstrated the following:

- spontaneous BRS was capable of detecting autonomic dysfunction earlier than conventional autonomic function tests [19, 34];
- spontaneous BRS showed greater sensitivity and specificity in the detection of autonomic dysfunction than conventional autonomic function tests [20, 35].

Pathophysiological theories of diminished BRS in diabetes mellitus

Although the exact pathomechanisms leading to reduced BRS in DM remain unclear, some evidence has linked the reduced BRS to diabetes-induced changes in the autonomic nervous system and its regulation of cardiovascular functions [11, 33, 36–40]. These changes which can occur at both the central and peripheral (afferent and efferent) levels of the baroreflex circuit (as shown in Fig. 1 and Table 1) lead to autonomic dysfunction (as indicated by a diminished BRS).

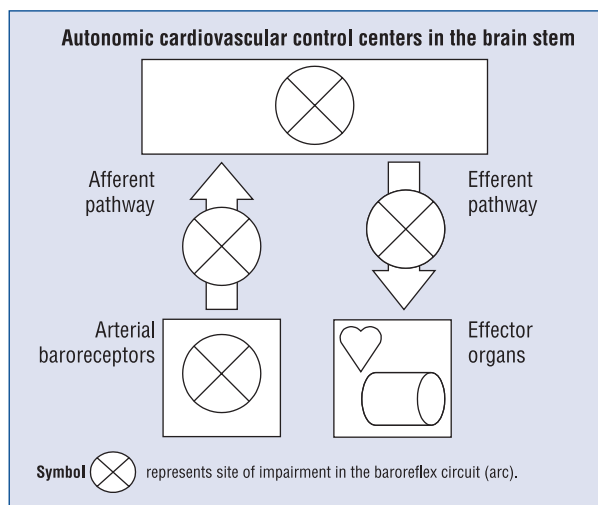


Figure 1. Impairments occurring at the different levels of the baroreflex circuit in diabetic patients.

Atherosclerosis may also contribute to BRS impairment at the baroreceptor level of the baroreflex circuit (Fig. 1, Table 1). Diabetes is a known risk factor for atherosclerosis [41]. As a matter of fact, atherosclerosis is both premature and accelerated in diabetic patients [41, 42]. Carotid atherosclerosis has been associated with depressed BRS [43–46]. In another study in type 2 DM patients, carotid atherosclerosis was linked to impaired BRS and CAN [47].

Features, clinical and prognostic consequences of diminished BRS in diabetes mellitus

Diabetic patients who have diminished BRS are characterized by the following features (see also section a of Table 2). They demonstrate:

Table 1. Diabetes-induced changes in the baroreflex circuit associated with diminished baroreflex sensitivity (BRS).

Level of baroreflex circuit	Author and reference	Specific location of impairment associated with diminished BRS	Brief description of impairment associated with diminished BRS
Arterial baroreceptors	Gianaros et al. [43]	Human carotid bulb (abundant in baroreceptors)	Increased IMT (a sign of subclinical atherosclerosis) associated with ↓ BRS
Afferent pathways	Clarke et al. [48]	Carotid sinus nerve (a branch of the glossopharyngeal) in diabetic rats	Diabetes-induced axonal and intramyelinic edema
	Fazan et al. [49]	Aortic depressor nerve (an afferent branch of the vagus) in STZ-induced diabetic rats	Diabetes-induced axonal atrophy of the nerve
	Li et al. [50–52]	NG in STZ-induced diabetic rats	↓ cell excitability of the aortic baroreceptor neurons in the NG resulting from overactivation of both the angiotensin II-NADPH oxidase superoxide signal pathway and the HCN channels
Efferent pathways	Gottsäter et al. [47]	Parasympathetic efferents in type 2 DM patients with CAN	Abnormal E/I ratio indicating structural damage in parasympathetic efferents
	Eckberg et al. [53]	Sympathetic efferents in DM patients	Abnormal sympathetic responses indicative of structural damages in the sympathetic efferent pathway
Autonomic cardiovascular control centers in the brainstem	Chen et al. [39]	NTS in STZ-induced diabetic rats	Diabetes-induced impairment in the NTS
	Yan et al. [40]	NA in diabetic mice	Diabetes-induced structural changes (reduction in the number of cardiac motor neurons in NA); diabetes induced functional changes (reduced regulation of heart rate by NA)

CAN — cardiovascular autonomic neuropathy; DM — diabetes mellitus; E/I — expiration/inspiration; HCN — hyperpolarization-activated cyclic nucleotide-gated; IMT — intima-media thickness; NA — nucleus ambiguus; NG — nodose ganglia; NTS — nucleus tractus solitarius; STZ — streptozotocin

Table 2. Features, clinical and prognostic consequences, prognostic determinants of diminished baroreflex sensitivity (BRS) in diabetes mellitus (DM).

<p>Features of diminished BRS in DM</p> <p>Presence of inflammatory markers in the plasma (e.g. hs-CRP)</p> <p>Insulin resistance/hyperinsulinemia</p> <p>Essential hypertension</p> <p>Microalbuminuria</p> <p>Hypoadiponectinemia</p> <p>Elevated BNP level</p> <p>More common prevalence of overt CAD, previous MI, previous CHF</p> <p>Clinical and prognostic consequences of diminished BRS in DM</p> <p>Increased morbidity and mortality from cardiac and non-cardiac causes</p> <p>Cardiac causes: CAD, hypertension, LVD with subsequent CHF, MI</p> <p>Noncardiac causes: cerebrovascular diseases (e.g. stroke), diabetic nephropathy</p> <p>Prognostic determinants in DM patients with diminished BRS</p> <p>Gender (female sex associated with lower BRS and worse prognosis)</p> <p>Disease duration</p> <p>Degree of autonomic imbalance/degree of BRS impairment and the potential for its reversal</p> <p>Presence and degree of CAN</p> <p>Presence of co-existing diseases especially those conditions already associated with depressed BRS such as hypertension, MI, CHF, obesity, insulin resistance, renal damage</p> <p>Extent of glycemic control</p> <p>Timely introduction and sustained use of appropriate BRS-improving interventions</p> <p>Presence and level of certain laboratory markers e.g. microalbuminuria/proteinuria, BNP level, hypoadiponectinemia, hs-CRP, HbA1c, etc.</p>
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BNP — brain natriuretic peptide; CAD — coronary artery disease; CAN — cardiovascular autonomic neuropathy; CHF — congestive heart failure; hs-CRP — high sensitivity C-reactive protein; HbA1c — glycated hemoglobin; LVD — left ventricular dysfunction; MI — myocardial infarction

- **The presence of low-grade inflammation (higher levels of plasma high-sensitivity C-reactive protein (hsCRP) [54]:** In type 2 DM patients, increased plasma levels of hsCRP have been associated with depressed cardiovascular autonomic function as indicated by diminished BRS [54]. Higher plasma levels of CRP have also been linked to insulin resistance, obesity (increased body mass index) and the development of type 2 DM, thereby suggesting the role of an underlying inflammatory process in the etiopathogenesis of diabetes [55–57].
 - **Insulin resistance/hyperinsulinemia:** Studies show that DM patients with insulin resistance/hyperinsulinemia have a reduced BRS [54, 58–60]. This association can perhaps be explained by the findings that insulin causes sympathetic nervous system activation [61, 62].
 - **Essential hypertension [59]:** Hypertension occurs more often in diabetic patients (especially in type 2 DM) than in nondiabetic patients with most hypertensive diabetic patients having essential hypertension [63].
- Impaired BRS could contribute to the development of hypertension in DM [64]. Also both essential hypertension and type 2 DM exert a combined synergistic effect that diminishes BRS [59]. Hypertension in diabetic patients has also been attributed to the actions of hyperinsulinemia in stimulating the sympathetic nervous system [61, 65].
- **Renal damage as evidenced by microalbuminuria:** In microalbuminuric type 1 DM patients, BRS was found to be depressed [66]. Studies in type 2 DM patients showed that the presence of microalbuminuria was characterized by both insulin resistance and cardiovascular autonomic dysfunction (as indicated by a diminished BRS, lower myocardial 123I-metaiodobenzylguanidine [MIBG] uptake, etc.) [58]. In addition, studies conducted in elderly type 2 DM patients showed that CAN and arterial BP were independently associated with microalbuminuria [67]. From the results of all these studies, one could hypothesize that sympathetic overactivity is perhaps the pathophysiological link between microalbumi-

nuria and diminished BRS. Microalbuminuria is an independent risk factor for cardiovascular events such as MI, stroke, cardiovascular death and congestive heart failure (CHF) in both diabetic and non-diabetic subjects [68].

- **Hypoadiponectinemia (decreased level of plasma adiponectin):** Adiponectins are proteins secreted by adipose tissues; they circulate in great amounts in the human plasma and play a role in glucose regulation (by reducing plasma glucose and improving insulin sensitivity in both healthy and diabetic subjects) and also in the catabolism of fatty acids [69]. Hypoadiponectinemia has been associated with insulin resistant states (such as type 2 DM and obesity), hypertension and vascular atherogenesis [60, 69–71]. In studies in type 2 DM patients, hypoadiponectinemia was found to be associated with increased cardiac sympathetic activity and therefore with a diminished BRS [60].
- **The presence of neurohormonal activation (high levels of plasma B-type natriuretic peptide (BNP) [72]:** BNP, a cardiac neurohormone can help identify diabetic patients at increased risk of developing left ventricular abnormalities [73]. Diminished BRS has been linked to left ventricular abnormalities (as indicated by an increased left ventricular mass index) in DM patients [74]. It has also been demonstrated that BNP can serve as a prognostic tool in DM patients, helping to identify those at increased risk of mortality from cardiovascular and other causes [75].
- **More common prevalence of overt coronary artery disease (as indicated by the need for revascularization) [76], previous MI and previous CHF:** BRS has been shown to be depressed in post-MI subjects [77–79].

Clinical and prognostic consequences of diminished BRS (see Table 2)

Diminished BRS in DM is associated with an increased risk of morbidity and mortality from cardiac and non-cardiac causes. One study using the BRS-Phe method in 184 patients (who had type 2 DM without structural heart diseases or any other severe complications) with a mean follow-up period of 4.7 years, linked diminished BRS to incidences of nonfatal MI, CHF, need for coronary revascularization, stroke and cardiovascular deaths [76]. The link between depressed BRS and renal disease (as indicated by microalbuminuria) has been discussed earlier.

In the Hoorn study [80] involving hundreds of subjects who had either DM, or hypertension or a history of cardiovascular disease with a 9 year follow-up period, it was shown that the mortality risk from cardiac and other causes was roughly twice greater in those who had DM and concomitant impairment in autonomic function (as evidenced by diminished BRS).

The prognostic determinants in DM patients with diminished BRS are outlined in Table 2. Female diabetic patients have been shown to have lower BRS and worse prognosis than their male counterparts [81]. Also, there exists a negative correlation between the disease duration and the BRS in diabetic patients [82]. Studies in DM patients have demonstrated that the degree of autonomic (sympathovagal) imbalance determines the extent of BRS impairment [82]. In addition, the extent of BRS impairment is also a determinant factor as a more depressed BRS has been associated with a poorer prognosis [81, 83]. Furthermore, as stated in an earlier section, CAN is associated with a more significantly depressed BRS [20] and therefore as can be expected a poorer prognosis. Also from a therapeutic point of view, abnormal autonomic tests (BRS inclusive) in patients with advanced CAN are less amenable to reversal by interventional modalities as will be discussed in the next section. Since BRS is reduced in CHF, hypertension, insulin resistance, obesity, and after MI as earlier stated, the co-existence of these disease conditions in a DM patient with an already depressed BRS increases the likelihood of an unfavorable prognosis. Improved glycemic control slows the progression of DM [84] and should therefore improve prognosis in such patients. BRS has also been correlated with HbA1c level [82].

Interventions improving BRS in patients with diabetes mellitus

Studies in experimental animal models and in diabetic patients have demonstrated an improved BRS following the use of pharmacological and nonpharmacological interventions (Table 3). Some other interventions (Table 4) have also been shown to be useful in ameliorating cardiovascular autonomic dysfunction in DM.

Clinical perspective on interventional modalities

Of all the interventional modalities listed in Table 3, physical (exercise) training seems to be the most effective in improving BRS. The importance of regular and sustained exercise regimen

Table 3. Interventions improving baroreflexsensitivity (BRS) in diabetic subjects.

Specific intervention	Study subjects with references	Duration of use of intervention	Major mechanism(s) by which intervention improved BRS	Added advantage(s) of intervention
Pioglitazone (a thiazolidinedione)	Type 2 DM patients with recent MI [85]	12 weeks of treatment	Sympathoinhibition resulting from the effects of the drug in decreasing insulin resistance	↑ level of plasma adiponectin; ↓ incidence of fatal and nonfatal MI
ALA-an antioxidant	STZ-induced diabetic rats [86]	At least 4 weeks treatment	↓ oxidative stress; reversal of DM-induced deficit in c-Fos-ir neurons in the NTS	Refer to Table 4
Leptin (an adipose tissue derived hormone)	Short-term STZ-induced diabetic rats [87]	7 days of continuous ICV infusion	Actions of leptin on the central nervous system to induce euglycemia	Normalization of plasma glucose; reversal of diabetes-induced hyperphagia
Fluvastatin (HMG-CoA reductase inhibitor)	STZ-induced type 1 diabetic rats [88]	30 days of treatment	Still to be determined, but perhaps connected to the effects of statins in up-regulating the expression of nNOS in the RVLM	Antilipemic, antioxidative, antiatherogenic and antithrombotic effects of the drug; improvement of impaired cardiac function
Lacidipine (a long-acting calcium channel blocker)	Hypertensive type 2 DM patients [89]	4 weeks of once daily treatment	↓ MABP and BPV	
Breathing exercise (slow, deep, controlled breaths, 6 breaths/min)	Type 1 DM patients with varying duration of disease [90]	Short (one-time maneuver during which BP and ECG were recorded)	Perhaps due to improved autonomic function resulting from the maneuver	↑ BRS in most patients studied (irrespective of disease duration), except in those with definite CAN
Physical training (exercise)	STZ-induced diabetic rats [91]	Single session of aerobic exercise	Not investigated in study	—
	STZ-induced diabetic rats [92]	10 weeks of treadmill exercise training	↑ baroreflex tachycardic and bradycardic responses	↑ chemoreflex sensitivity
	Type 2 DM patients [93]	12 months (of twice weekly endurance and muscle strength training sessions)	May be connected to exercise-induced improvements in endothelial function and endoneurial circulation	↑ glycemic control; ↑ exercise capacity; ↑ muscle strength
	Type 2 DM patients with concomitant hypertension and hypercholesterolemia [94]	3 months (of thrice weekly aerobic exercise)	Not investigated in study	—

ALA — alpha-lipoic acid; BP — blood pressure; BPV — blood pressure variability; CAN — cardiovascular autonomic neuropathy; c-Fos-ir — c-Fos-immunoreactive; DM — diabetes mellitus; ECG — electrocardiography; HMG-CoA — 3-hydroxy-3-methylglutaryl coenzyme A; ICV — intracerebroventricular; MABP — mean arterial blood pressure; MI — myocardial infarction; nNOS — neuronal nitric oxide synthase; NTS — nucleus tractussolitarius; RVLM — rostral ventrolateral medulla; STZ — streptozotocin

in the management of the cardiovascular risks associated with DM cannot be overemphasized. Regular exercise has been shown to improve HRV

parameters in patients with CAN (Table 4) with a deterioration of those parameters within weeks of complete exercise withdrawal [109].

Table 4. Interventions ameliorating cardiovascular autonomic dysfunction in diabetes mellitus (as indicated by other autonomic markers such as heart rate variability [HRV]).

Intervention	Study type and/or subjects involved with reference(s)	Duration of use/duration of study of intervention	Effect(s) of intervention
Insulin	Type 2 DM patients on oral antidiabetic drugs [95]	4 months follow-up of daily insulin administration	↑ HRV
	Type 1 DM patients with varying degrees of CAN [96]	12 months of intensive insulin therapy	↑ HRV in patients with early CAN
	Type 1 DM patients who received intensive insulin therapy — DCCT study [97]	Average follow-up of 6.5 years	Intensive insulin therapy slowed down the incidence and progression of abnormal autonomic tests
	14 years follow-up study in former DCCT intensive insulin therapy patients [98]		↓ incidence of CAN in former intensive insulin patients for even up to 14 years after DCCT completion
Metformin	Obese type 2 DM patients [99]	4 months of metformin + diet	↑ cardiac sympathovagal balance (as indicated by ↑ HRV parameters)
Quinapril (ACEI)	DM patients with and without DAN [100]	6 months follow-up using quinapril	↑ total HRV and ↑ parasympathetic functions in the early stages of DAN
Losartan (ARB) and/or Quinapril	Patients with longstanding DM (type 1 and 2) and DAN [101]	12 months of either or both drugs	↑ cardiac function with early treatment using either of both drugs; ↑ efficacy with combination therapy
Metoprolol (β-blocker)	ACEI-treated type 1 DM patients with albuminuria [102]	6 weeks of metoprolol	↑ autonomic function (↑ HRV) upon addition of metoprolol to treatment regimen
Atenolol (β-blocker)	Type 1 DM patients with ↓ HRV and detectable hs-CRP [103]	3–4 weeks of atenolol	↑ HRV and ↑ hs-CRP levels in atenolol-treated patients
Epalrestat (an ARI)	Type 2 DM patients with DAN [104]	3 months or more	↑ HRV
ALA, antioxidant	Type 2 DM patients with CAN [105, 106]	4 months of ALA	Amelioration of CAN to some degree
XNT (ACE2 activator)	STZ-induced diabetic rats [107]	30 days of XNT	Protected against diabetes-induced cardiovascular autonomic dysfunction
Vitamin E (antioxidant)	Type 2 DM patients [108]	4 months	↑ cardiac sympathovagal balance (as indicated by ↑ HRV parameters) on long-term treatment
Physical training (exercise)	DM patients with and without CAN [109]	12 weeks (of twice weekly exercise of 30 min duration)	↑ HRV in patients without CAN and in those with early CAN but not in those with advanced CAN; deterioration of previously improved HRV parameters following 6 weeks of exercise withdrawal
	Type 2 DM patients with and without CAN [110]	6 months (of thrice weekly exercise)	Improvement in some HRV parameters in both groups of patients with greater benefits in those with definite CAN; positive effects on lipid profile, plasma glucose and HbA1c in both groups

ACEI — angiotensin converting enzyme inhibitor; ACE2— angiotensin converting enzyme 2; ALA — alpha-lipoic acid; ARB — angiotensin receptor blocker; ARI — aldose reductase inhibitor; CAN — cardiovascular autonomic neuropathy; DAN — diabetic autonomic neuropathy; DCCT — diabetes complication and control trial; DM — diabetes mellitus; HbA1c — glycated hemoglobin; hs-CRP — high sensitivity C-reactive protein; STZ — streptozotocin; XNT — 1-[(2-dimethylamino)ethylamino]-4-(hydroxymethyl)-7-[(4-methylphenyl) sulfonyl oxy]-9H-xanthene-9-one

Pioglitazone [85] as a BRS-improving agent particularly appears to be useful in post-MI type 2 DM patients due to its cardioprotective functions. Breathing exercise [90] also appears to be useful in improving BRS in DM patients regardless of the duration (except of course in those with marked CAN). Alpha-lipoic acid (ALA) shows promise in potentially improving BRS in diabetic patients due to the results already obtained in experimental models [86]. ALA has also been shown to ameliorate CAN to some extent in type 2 DM patients [105, 106]. Statins (HMG-CoA reductase inhibitors) have proven to be a useful addition to treatment regimens in DM patients with co-existing cardiovascular risk factors [111]. Due to the beneficial effects of fluvastatin in improving BRS in STZ-induced diabetic rats [83], statins appears to be potentially useful in ameliorating baroreflex impairment in diabetic patients at both the medullary level (through their effects in up-regulating the expression of neuronal nitric oxide synthase, nNOS [83, 112]) and at the baroreceptor level (through their effects in causing atherosclerotic plaque regression [113]). Leptin [87] still appears experimental at this stage; therefore there is need for more studies in order to ascertain its efficacy in improving BRS in diabetic patients. Perhaps the interventions listed in Table 3 may be more effective in improving BRS when they are combined together rather than when used individually; this hypothesis clearly warrants further studies in order to confirm if combination therapy (or multifactorial intervention) has these synergistic effects. There is also a need to further study these interventions (Table 3) in patients with depressed BRS that is accompanied by marked DAN to see if these interventions will still remain effective in improving BRS and in ameliorating the manifestations of autonomic neuropathy.

The pharmacological agents shown in Table 4 such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, metformin, aldose reductase inhibitors, angiotensin converting enzyme-2 activators, etc., should also be further investigated in the context of their capability for improving BRS in diabetic patients.

Finally, there is a need for extensive follow-up studies in diabetic patients in order to determine if the gains (e.g. improved BRS and amelioration of cardiovascular autonomic dysfunction, etc.) obtained from the above mentioned interventions do translate into better clinical and prognostic outcomes (in terms of reduced cardiovascular morbidity and mortality) for such patients.

Conclusions

The key to success with diabetes and its complications is early diagnosis and immediate and ongoing treatment plans. With early diagnosis of baroreflex impairment in DM using the assessment methods outlined above and quick establishment of effective treatment plans, it is potentially possible to improve BRS and slow the progression of cardiovascular autonomic dysfunction in such patients.

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