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REVIEW: Cardiovascular Autonomic Neuropathy Due to Diabetes Mellitus: Clinical Manifestations, Consequences, and Treatment

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Context: The aim of this article was to review the importance of the clinical identification of persons with cardiovascular autonomic neuropathy (CAN) and discuss potential treatment interventions.

Evidence Acquisition: A MEDLINE search was conducted for articles published during the last 20 yr. In addition, subsequent references of retrieved articles were reviewed. Search strategies included using key terms such as CAN, heart rate variability, orthostatic hypotension, and diabetes mellitus.

Evidence Synthesis: CAN is a common form of diabetic autonomic neuropathy and causes abnormalities in heart rate control as well as central and peripheral vascular dynamics. The clinical manifestations of CAN include exercise intolerance, intraoperative cardiovascular lability, orthostatic hypotension, painless myocardial ischemia, and increased risk of mortality. CAN contributes to morbidity, mortality, and reduced quality of life for persons with diabetes. The American Diabetes Association has recently published a statement that provides guidelines for prevention, detection, and management of neuropathy, including CAN, for healthcare providers who care for patients with diabetes. Algorithms for the evaluation and treatment of the patient with CAN, even if the patient is asymptomatic, are provided in this review.

Conclusions: Once CAN is identified in a patient with diabetes, healthcare providers may consider altering the prescribed exercise regimen, increasing surveillance for cardiac ischemia, carefully reexamining the list of prescribed medications, and aggressively treating cardiovascular risk factors (*e.g.* hypertension) that may be associated with the development of CAN. **(*J Clin Endocrinol Metab* 90: 5896–5903, 2005)**

THE AUTONOMIC NERVOUS system modulates the electrical and contractile activity of the myocardium via the interplay of sympathetic and parasympathetic activity (1). An imbalance of autonomic control is implicated in the pathophysiology of arrhythmogenesis (1). Cardiovascular autonomic neuropathy (CAN), a common form of autonomic dysfunction found in patients with diabetes mellitus, causes abnormalities in heart rate control, as well as defects in central and peripheral vascular dynamics. Individuals with parasympathetic dysfunction have a high resting heart rate most likely because of vagal neuropathy that results in unopposed increased sympathetic outflow. Persons with a combined parasympathetic/sympathetic dysfunction have slower heart rates. With advanced nerve dysfunction, heart rate is fixed. Thus, it is apparent that the determination of heart rate itself is not a reliable diagnostic sign of CAN. Reduction in variability of heart rate is the earliest indicator of CAN. Clinical manifestations of CAN include exercise intolerance, intraoperative cardiovascular lability, orthostatic hypotension (OH), asymptomatic ischemia, painless myocardial infarction (MI), and increased risk of mortality (2). A recent publication by the American Diabetes Association highlighted the significance of diabetic neuropathy by issuing a statement for healthcare professionals that provides guidelines for prevention, detection, and management of neuropathy (3). In light of the statement by the American Diabetes Association, we discuss in this overview the clinical manifestations, consequences of, and therapeutic strategies for CAN in diabetic patients.

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Abbreviations: ACE, Angiotensin converting enzyme; ARI, aldose reductase inhibitor; AT_1, angiotensin type 1; CAN, cardiovascular autonomic neuropathy; FFA, free fatty acid; HRV, heart rate variability; MI, myocardial infarction; OH, orthostatic hypotension.

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Clinical Manifestations of Cardiovascular Autonomic Dysfunction

Exercise intolerance

In diabetic individuals with CAN, exercise tolerance is limited as a result of impaired parasympathetic/sympathetic responses that would normally enhance cardiac output and result in directing peripheral blood flow to skeletal muscles (4). Reduced ejection fraction, systolic dysfunction, and decreased diastolic filling, potentially as a result of CAN, also limit exercise tolerance (4). For diabetic persons likely to have CAN, it has been suggested that cardiac stress testing should be performed before beginning an exercise program (5). When discussing exercise instructions and goals with patients with CAN, healthcare providers need to emphasize that the use of heart rate is an inappropriate gauge of exercise intensity because maximal heart rate is depressed in persons with CAN (6). Recently it has been shown that percentage of heart rate reserve, an accurate predictor of percentage of VO_2

reserve, can be used to prescribe and monitor exercise intensity in diabetic individuals with CAN (7). An alternate method for monitoring intensity of physical activity is the Rating of Perceived Exertion scale (7, 8). The Rating of Perceived Exertion scale, which uses the subjective feelings of intensity of the individual, can be used in clinical settings where maximal heart rate is not easily measured.

Intraoperative cardiovascular lability

There is a 2- to 3-fold increase in cardiovascular morbidity and mortality intraoperatively for patients with diabetes (9). Studies have demonstrated that the induction of anesthesia causes a greater degree of decline in heart rate and blood pressure in diabetic patients compared with nondiabetic individuals (10) and that hemodynamic stability, in the intraoperative period, depends on the severity of autonomic dysfunction (11). Patients with severe autonomic dysfunction have a high risk of blood pressure instability (11, 12), and intraoperative blood pressure support is needed more often in those with greater impairment (10). Intraoperative hypothermia (13), which may decrease drug metabolism and affect wound healing, and impaired hypoxic-induced ventilatory drive (14) have also been shown to be associated with the presence of CAN. Although one study failed to detect any association with abnormal hemodynamics during anesthesia in patients with diabetic CAN and coronary artery disease (15), noninvasive diagnostic methods assessing autonomic function allow identification of at-risk patients preoperatively and may better prepare the anesthesiologist for potential hemodynamic changes.

Orthostatic hypotension

A change from lying to standing normally results in activation of a baroreceptor-initiated, centrally mediated sympathetic reflex, resulting in an increase in peripheral vascular resistance and cardiac acceleration (9). OH is characterized by a defect in this reflex arc, resulting in signs and symptoms such as weakness, faintness, dizziness, visual impairment, and syncope. Although the absolute fall in blood pressure is arbitrary, OH is usually defined as a fall in blood pressure [*i.e.* >20–30 mm Hg for systolic or >10 mm Hg for diastolic (16, 17)] in response to postural change, from supine to standing.

Painless myocardial ischemia

Inability to detect ischemic pain can impair the recognition of myocardial ischemia or MI. The mechanisms of painless myocardial ischemia are, however, complex and not fully understood. Altered pain thresholds, subthreshold ischemia not sufficient to induce pain, and dysfunction of the afferent cardiac autonomic nerve fibers have all been suggested as possible mechanisms (18). A recent investigation that used positron emission tomography to measure regional cerebral blood flow as an index of regional neuronal activation has shown that impaired afferent signaling resulting from autonomic dysfunction is associated with failed signal transmission from the thalamus to the frontal cortex (19). Although evidence for a mechanistic link between diabetes and painless myocardial ischemia may not include autonomic dysfunction as some have suggested (20), it is hard to ignore the results of the Detection of Ischemia in Asymptomatic Diabetics study (21). In the Detection of Ischemia in Asymptomatic Diabetics study of 1123 patients with type 2 diabetes, cardiac autonomic dysfunction was a strong predictor of ischemia (21). A meta-analysis of 12 studies also demonstrated a consistent association between CAN and the presence of painless myocardial ischemia (2). The Mantel-Haenszel estimate for the pooled prevalence rate risk for silent myocardial ischemia was 1.96, with a 95% confidence interval of 1.53–2.51 ($P < 0.001$; n = 1468 total subjects) (2). Thus, patients with CAN warrant more careful attention. Cardiovascular autonomic function testing may be an important component in the risk assessment of diabetic patients with coronary artery disease (21).

Increased risk of mortality

Impaired autonomic control of heart rate is linked to increased risk of mortality. Reduced parasympathetic function or increased sympathetic activity may provide the propensity for lethal arrhythmias (22). In a recent meta-analysis of 15 studies among individuals with diabetes, CAN was found to be significantly associated with subsequent mortality when autonomic dysfunction was defined as the presence of two or more abnormalities of tests of heart rate variability (HRV) [*i.e.* pooled relative risk was 3.45 (95% confidence interval, 2.66–4.47; $P < 0.001$)] (23). The stronger association observed in studies defining CAN by the presence of two or more abnormalities may be due to more severe autonomic dysfunction in these individuals, specificity of assessment modalities, or a higher frequency of other comorbid complications.

Measurement of Cardiovascular Autonomic Function

A complete discussion of various assessment modalities of cardiovascular autonomic function has been examined in an earlier technical review (2). Table 1 provides a brief description of three assessment modalities (24–27) that were recommended for longitudinal testing of cardiovascular autonomic function by a consensus conference (28).

Treatment Interventions to Ameliorate Cardiovascular Autonomic Dysfunction via Pharmacological Agents

Interventions to ameliorate reduced HRV are being evaluated in clinical trials based on theories of the pathogenesis of diabetic neuropathy. Development of diabetic neuropathy is the result of a multifactorial process including metabolic insult to nerve fibers, neurovascular insufficiency, increased oxidative stress, reduction in neurotrophic growth factors, deficiency of essential fatty acids, formation of advanced glycosylation end products, and autoimmune damage (2). Various pharmacological agents that are directed at components of the pathogenic process are described below.

Glycemic control

The results of the Diabetes Control and Complications Trial showed that intensive treatment prevented the devel-

TABLE 1. Modalities used for the assessment of cardiovascular autonomic function

Assessment modality	Description of the assessment modality
RR variation	Degree of RR variation represents the magnitude of sinus arrhythmia and is, for the most part, under control of the parasympathetic nervous system. There are several different methods to measure the amount of RR variation reported in the literature including standard deviation, coefficient of variation, mean circular resultant (MCR), maximum minus minimum, expiration/inspiration ratio, and spectral analysis (24). It should be noted that standard deviation, coefficient of variation, maximum minus minimum, and expiration/inspiration ratio are affected by ectopic beats. Spectral analysis is found more often in research settings. MCR is probably the most appropriate one (25, 26). The MCR is determined by vector analysis, and the length of the vector mean is proportional to the amount of HRV. Genovely and Pfeifer provide a complete discussion of the determination of the MCR (27). RR variation is age dependent.
Valsalva maneuver	The Valsalva maneuver is more of a generalized test of autonomic function because a greater degree of autonomic impairment is required before abnormalities are demonstrated.
Postural blood pressure response	The response in blood pressure when an individual goes from the supine position to standing is regarded mainly as a measure of sympathetic function.

opment of abnormal RR variation and slowed the deterioration of autonomic dysfunction over time (29). Eighteen years of follow-up of a group of type 1 diabetic individuals demonstrated that fair long-term glycemic control (*i.e.* glycosylated hemoglobin $< 8.4\%$) was associated with preserved cardiovascular autonomic function, whereas lack of fair glycemic control was associated with dysfunction (30). For persons with type 2 diabetes, intensive insulin therapy showed a small tendency for improved autonomic function, whereas deterioration was noted in the conventionally treated group (31).

Antioxidants

During chronic hyperglycemia, the metabolism of glucose also results in the generation of free radicals. Although free radicals of superoxide and hydrogen peroxide are essential for normal cell function, excessive accumulation of free radicals is detrimental and has a direct neurotoxic effect (32). α-Lipoic acid, an antioxidant that reduces free radical formation, appears to slow progression of CAN (33, 34). For persons with type 2 diabetes, the improvement in CAN was seen after 4 months of treatment with an oral dosage of 800 mg/d (34). For persons with type 1 diabetes, the effect on autonomic function was seen after 10 d of 600 mg daily iv α-lipoic acid followed by 600 mg given orally for 50 d (33). It should be noted that many herbal manufacturers are promoting α-lipoic acid for use by patients with diabetes, but studies evaluating the effectiveness of these products have not been performed. Vitamin E has been shown to improve the ratio of cardiac sympathetic to parasympathetic tone for persons with type 2 diabetes (35). In light of a recent meta-analysis that found that 400 IU/d or more may increase all-cause mortality, high doses of vitamin E should be avoided (36).

Angiotensin converting enzyme (ACE) inhibitors

Microvascular insufficiency has also been proposed as a potential component in the pathogenesis of diabetic neuropathy. Results of animal studies have suggested that impaired ganglion blood flow in diabetes could be responsible for neurodegenerative changes in autonomic postganglionic cell bodies (37). In human diabetic neuropathy, impaired nerve blood flow has been demonstrated (38). Given that vascular dysfunction may be part of the pathogenesis of diabetic neuropathy, ameliorating this abnormality may positively benefit nerve function. ACE inhibitors promote vasodilation by preventing the generation of angiotensin II and by preventing the breakdown of bradykinin. Angiotensin II, in addition to its role as a vasoconstrictor, stimulates aldosterone release and promotes sympathetic outflow, thus ACE inhibitors may provide additional benefits as a result of the inhibition of angiotensin II. With regard to changes in HRV, the use of ACE inhibitors in patients with CAN has resulted in conflicting outcomes. Of the ACE inhibitors studied, 12 months of use of quinapril showed some degree of success in treating CAN (39), whereas no improvement of cardiovascular autonomic function was shown after 12 months of treatment with trandolapril (40). Conflicting results from various studies are disappointing, but it is important to remember that the effect of medications might not be homogeneous, even within the same class, and the beneficial response of an ACE inhibitor may depend on the degree of tissue penetration (41).

Angiotensin type 1 blockers

Angiotensin type 1 (AT_1) receptor mediates all potentially deleterious effects of angiotensin II (42). AT_1 antagonists block the AT_1 receptor, thus blocking the harmful effects of angiotensin II. We conducted a 1-yr clinical trial in 44 diabetic individuals to determine the effect of losartan on HRV. We hypothesized that losartan would improve nerve function by increased nerve blood flow and inhibition of angiotensin II-induced facilitation of sympathetic neurotransmission. Although 50 mg of losartan appeared to slow the expected decline in RR variation, there was no significant improvement (43). Improved cardiovascular autonomic function was, however, shown in another study, in which 23 diabetic individuals were treated with 100 mg of losartan for 1 yr (44). Twelve weeks of treatment of losartan (50–100 mg/d) was also shown to reduce muscle sympathetic activity and improve cardiac baroreceptor sensitivity for 10 nondiabetic males with hypertension (45). In contrast, a 7-d trial in nondiabetic males treated with eprosartan was shown to lower HRV (46).

Aldosterone blockers

Aldosterone has been shown to affect the autonomic nervous system with sympathetic activation and parasympathetic inhibition (47) and impair the baroreflex response (48). Other dysfunctions associated with aldosterone include the blockage of myocardial uptake of norepinephrine in animal models (49) and decreased arterial and venous compliance, leading to vascular organ damage (50). Spironolactone, an aldosterone-receptor blocker, has been used to reduce the morbidity and mortality for patients with severe heart failure (47). Mechanisms thought to promote the beneficial effect of spironolactone include blocking the effect of aldosterone on the loss of potassium and magnesium and improved HRV (51–53). For example, acute administration of an aldosterone antagonist given iv has been shown to improve HRV and baroreflex sensitivity in healthy subjects, suggesting that aldosterone exerts a tonic inhibitory effect on cardiac vagal control (54). In disease-specific studies, the use of spironolactone improved HRV and survival for patients with congestive heart failure (51–53). In contrast, however, one study of individuals with type 2 diabetes administered spironolactone 50 mg/d for 1 month demonstrated a small but significant worsening in HRV (55). It is possible that the effects of spironolactone may be disease specific. To the best of our knowledge, eplerenone, a selective aldosterone blocker, has not been used to determine its effect on HRV in diabetic individuals.

Calcium-channel blockers

Calcium-channel blockers prevent the flow of calcium ions into cardiovascular cells by binding to the α_1 subunit of the L-type voltage-gated calcium channel (56). The drug class is heterogenous, however, with reflex sympathetic activation after blood pressure reduction occurring more frequently after blockade with dihydropyridines than phenylalkylamines (56). In studies of hypertensive individuals, verapamil depressed sympathetic activity (56), and slow release diltiazem had favorable effects on autonomic function (57). Verapamil also decreased norepinephrine excretion in persons with stable angina pectoris (58) and improved parasympathetic function in nondiabetic patients after an acute MI (59). Although the mechanism by which verapamil influences HRV is not clear, it may be due to specific properties of the drug that have a suppressive effect on sympathetic outflow of catecholamines (59). Calcium-channel blockers may not, however, have a beneficial effect on HRV in persons with diabetes. For example, verapamil had no effect on HRV in diabetic subjects post-MI (59), whereas long-acting calcium antagonists enhanced, rather than reduced, sympathetic activity in patients with type 2 diabetes (60).

β-Blockers

The use of β-blockers in diabetic patients has been questioned because these agents may mask signs and symptoms of hypoglycemia and interfere with insulin release. Nonetheless, in the Cooperative Cardiovascular Project, post-MI diabetic patients treated with β-blockers had a 36% reduction in mortality (61). In addition, β-blockers were associated with a lower 1-yr mortality rate for elderly diabetic patients (62). The exact reason for the reduction in mortality may or may not be related to the effect on CAN. In the β-blocker Heart Attack Trial, propranolol improved recovery of parasympathetic tone and decreased morning sympathetic predominance for post-MI patients (63). The addition of metoprolol to ramipril-treated type 1 diabetic patients with abnormal albuminuria was also shown to improve autonomic dysfunction (64).

Metformin

Free fatty acids (FFAs) interfere with glucose metabolism (65). Under normal circumstances, FFAs are the main fuel source for the heart (66). Recently, it has been shown that the combination of TNF-α and hyperglycemia stimulated lipolysis with a consequential increase in FFAs and induced insulin resistance (67). Decreased activation of the parasympathetic nervous system increases lipolysis, thus resulting in an increased concentration of FFAs in the plasma (66). An increase in FFAs has been shown to affect the cardiovascular system through activation of the sympathetic nervous system in healthy subjects (68), as well as in individuals with type 2 diabetes (69). Recently, it was demonstrated that overweight type 2 diabetic patients had metformin-related decreases in FFAs and insulin resistance that were associated with improved sympathovagal balance (70).

Treatment Interventions to Ameliorate Cardiovascular Autonomic Dysfunction via Nonpharmacological Agents

It is well known that exercise plays an important role in the treatment of diabetes. The role of exercise in the improvement of cardiovascular autonomic function is not as clear. Numerous studies both in diabetic and nondiabetic populations have tried to determine whether HRV can be improved by exercise. For example, chronic endurance exercise training in sedentary adult males (71) and a single bout of submaximal endurance exercise in healthy males (72) were associated with increased HRV with a shift toward parasympathetic influence on cardiovascular function. Endurance training was also shown to improve vagal activity in nondiabetic patients who had a MI (73) and in insulin-requiring diabetic individuals with early CAN (74). Other studies showed no benefit or only minimal benefit for healthy men (75) and individuals with type 2 diabetes (76). The discordant findings are most likely due to differences in patient populations, lack of randomization, differences in length and type of exercise, and various measurements of autonomic function. Thus, more intervention studies are needed to determine the best exercise protocol that results in improved autonomic function for diabetic persons with CAN. In addition, it will be important to evaluate whether beneficial effects in autonomic function result in favorable effects on the clinical outcome (*e.g.* better exercise tolerance, decreased mortality) of these patients.

A suggested paradigm for treating diabetic individuals with autonomic dysfunction using both nonpharmacological and pharmacological agents is provided in Fig. 1. An assessment for microalbuminuria is included in the paradigm

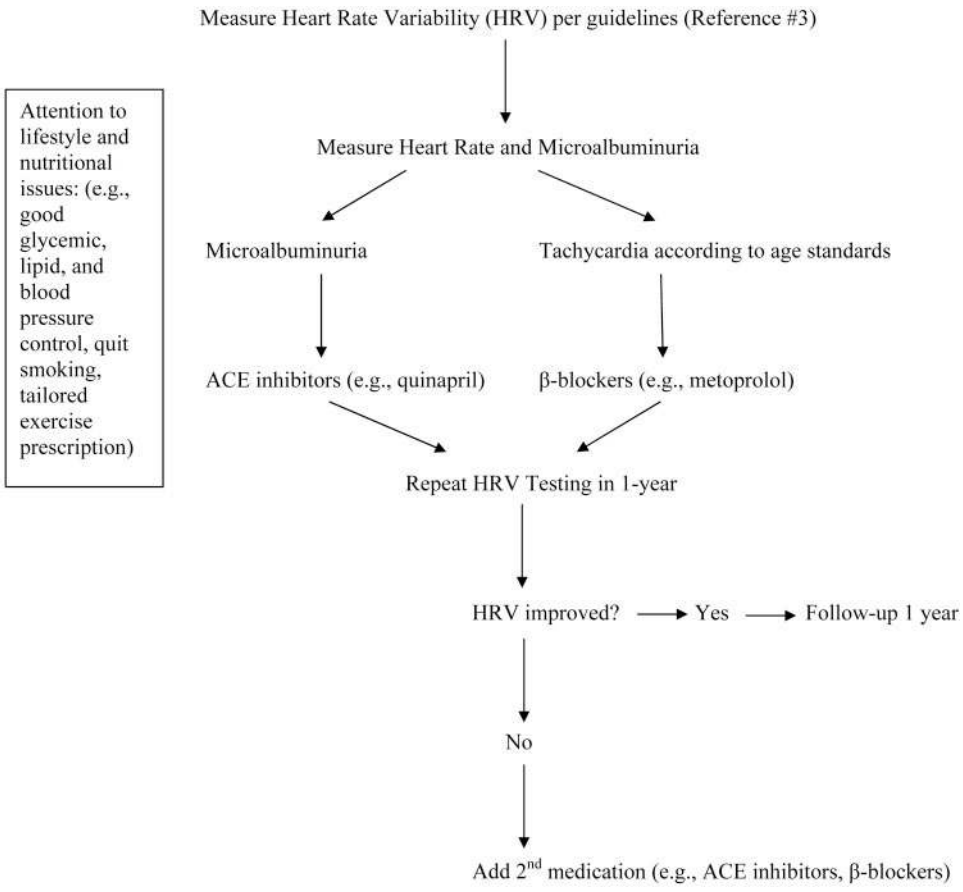

FIG. 1. Paradigm for treating diabetic individuals with cardiovascular autonomic dysfunction. Starting doses of all the medications mentioned in this review would have to be individualized for the patient considering the presence of other comorbid conditions. Patients would need to be followed closely with titration of medications determined according to individualized needs.

based on studies that have shown an association between CAN and microalbuminuria (77–79). Although a cause-effect relationship has not been proven, it is hypothesized that impairment of autonomic function is involved in the pathogenesis of diabetic nephropathy (77). The use of ACE inhibitors in the treatment of microalbuminuria is well established, and ACE inhibitors have been shown in some studies to improve HRV (39).

Investigational Medications for Potential Use for Cardiovascular Autonomic Dysfunction

Aldose reductase inhibitors

Chronic hyperglycemia causes activation of the polyol pathway with the accumulation of sorbitol and fructose, resulting in various metabolic imbalances that lead to neuronal dysfunction (80). In the early 1980s, aldose reductase inhibitors (ARIs), which reduce activity in the polyol pathway, generated hope with regard to the potential treatment of diabetic neuropathy. Due to lack of safety and/or efficacy, however, several ARIs have been withdrawn from the market and currently no ARIs are available for use in the U.S. One ARI (*i.e.* epalrestat) has been marketed in Japan since 1995. Whereas two studies have shown improved measures of CAN with epalrestat administration (81, 82), another study showed no effect of epalrestat on cardiac sympathetic dysfunction (83). Recent results of a multicenter trial using zopolrestat indicated that measures of parasympathetic activity were not affected after 1 yr of treatment (84). Newer agents such as fidarestat and AS-3201 are being investigated in ongoing clinical trials assessing peripheral neuropathy.

Treatment Interventions for OH

Treatment of OH comprises nonpharmacological and pharmacological measures. Nonpharmacological measures, such as increasing consumption of water (85) and wearing lower-extremity stockings, can be used to reduce symptoms (*e.g.* dizziness, dyspnea) (86). When treating OH due to autonomic dysfunction, pharmacological therapies must balance an increase in standing blood pressure against prevention of supine hypertension (86). In addition, OH can be aggravated by different forms of therapy [*e.g.* tricyclic antidepressant (amitriptyline)] used for the treatment of other complications (*e.g.* painful sensory neuropathy). Therefore, careful attention to other medications that may aggravate OH in these patients is necessary (87).

A suggested paradigm for treating diabetic individuals with OH is provided in Fig. 2. Medications that expand the plasma volume (fludrocortisone) or those that supplement α adrenergic activity (midodrine) are the main pharmacological agents used in the treatment of OH. The dose needed to achieve a clinical benefit may, however, be accompanied by side effects. Octreotide, an somatotropin release-inhibiting hormone analog, in combination with midodrine acts synergistically to reduce the hypotensive effects of the ingestion of food and standing in individuals with autonomic dysfunction (88). Treatment with erythropoietin of OH in anemic

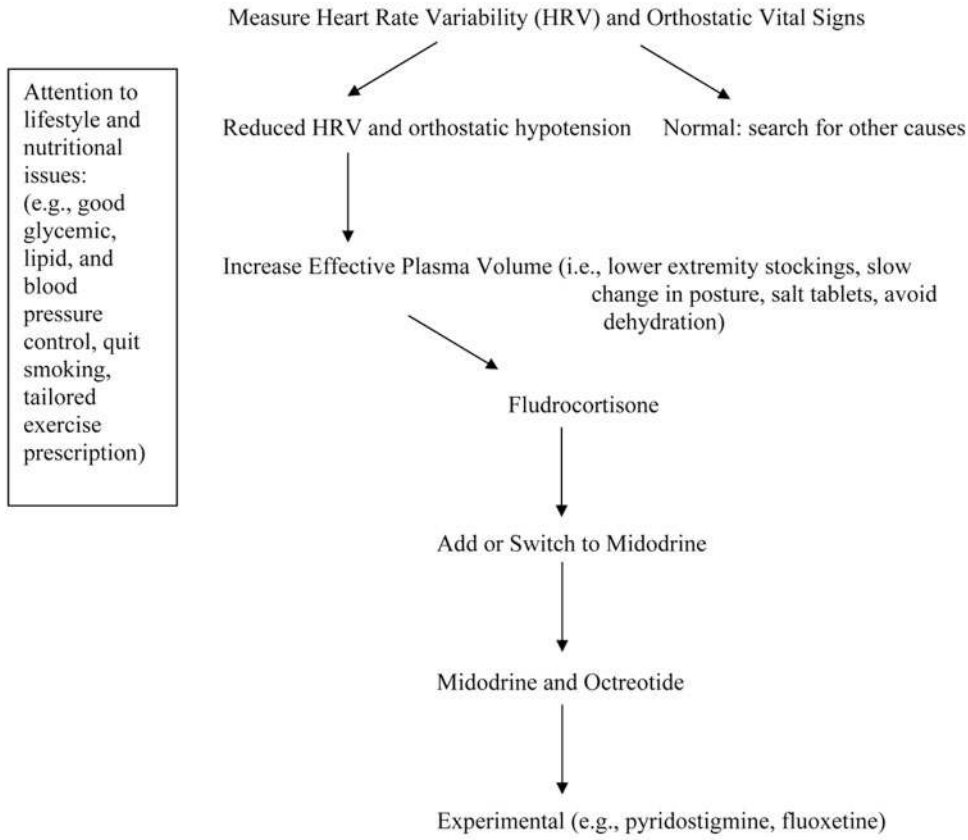

FIG. 2. Paradigm for treating diabetic patients with OH. When assessing and treating OH in patients with diabetes, it is important to keep in mind that autonomic neuropathy is not the only cause of OH in patients with diabetes. Thus, it is important to evaluate the patient for causes that may not be related to diabetes.

type 1 diabetic individuals with CAN has been shown to increase standing blood pressure (89). Recently, some novel approaches using other pharmacological agents have been investigated in nondiabetic individuals with OH. Enhancement of ganglionic transmission via the use of pyridostigmine (inhibitor of acetylcholinesterase) improved symptoms and orthostatic blood pressure with only modest effects in supine blood pressure for 15 patients with OH from numerous causes (90). Pyridostigmine has also been shown to improve HRV in healthy young adults (91). Fluoxetine, a selective serotonin reuptake inhibitor, improved hemodynamic parameters and symptoms of OH in patients with Parkinson's disease (92). Animal studies indicate that enhanced baroreflex control of sympathetic nerve activity may be a possible mechanism for improved orthostatic tolerance as a result of treatment with fluoxetine (93). Clonidine, a centrally acting α-agonist hypotensive agent, has been successfully used in a few patients with symptomatic OH concomitant with supine hypertension (94). Investigation of agents for diabetic persons with OH that reduce supine hypertension is of particular importance.

Summary and Conclusions

A number of different therapeutic agents are emerging for the treatment of diabetic neuropathy. Not all investigational drugs (*e.g.* antiglycation agents, protein kinase C β inhibitors, neurotrophic agents) have, however, been studied with regard to the effect on autonomic nerve-fiber function. Nonetheless, given the multifactorial process involved in the pathogenesis of diabetic neuropathy, it is likely that combination therapies directed at various components of the pathogenic pathway may be required. For persons with type 2 diabetes, intensive multifactorial treatment (*e.g.* targeting hyperglycemia, hypertension, dyslipidemia, and microalbuminuria) has been shown to reduce the risk of developing autonomic neuropathy (95). In addition, given the results of the European Diabetes Prospective Complications Study, which suggested that vascular factors (*e.g.* hypertension) may accelerate the adverse effects of hyperglycemia on nerve function, multifactorial intervention trials with diabetic neuropathy and CAN as primary outcomes appear warranted for individuals with diabetes (96–98). The concept of treating patients with asymptomatic CAN may not appeal to some physicians, particularly in light of the fact that there are no outcome data from clinical trials yet. However, given that the pathogenesis of neuropathy is affected by more than just glycemic control, we should endeavor to aggressively treat other risk factors, so as to prevent the onset and progression of complications, CAN being one of them.

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