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Recognizing and treating diabetic autonomic neuropathy

■ ABSTRACT

Diabetic autonomic neuropathy can cause heart disease, gastrointestinal symptoms, genitourinary disorders, and metabolic disease. Strict glycemic control can slow the onset of diabetic autonomic neuropathy and sometimes reverse it. Pharmacologic and nonpharmacologic therapies are available to treat symptoms.

■ KEY POINTS

The diagnosis of autonomic neuropathy is one of exclusion.

Cardiovascular complications include abnormal heart-rate control and orthostatic hypotension, with an increased risk of death.

Gastrointestinal symptoms include dysphagia, abdominal pain, nausea, vomiting, malabsorption, fecal incontinence, diarrhea, and constipation.

Erectile dysfunction is an early genitourinary symptom that may also signal cardiovascular problems.

Unawareness of hypoglycemia and unresponsiveness to it are the most troublesome metabolic complications because they impair the patient's ability to manage the disease.

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DIABETIC AUTONOMIC NEUROPATHY is a stealthy complication of diabetes, developing slowly over the years and quietly robbing diabetic patients of their ability to sense when they are becoming hypoglycemic or having a heart attack.

It can affect any organ of the body, from the gastrointestinal system to the skin, and its appearance portends a marked increase in the mortality risk of diabetic patients.

Intensive glycemic control is critical in preventing the onset and slowing the progression of diabetic autonomic neuropathy. The Diabetes Complications and Control Trial (DCCT) showed that intensive glycemic control reduced the prevalence of autonomic dysfunction by 53%.¹ It is also the first therapy to be considered when diabetic autonomic neuropathy is diagnosed. In addition, a variety of pharmacologic and nonpharmacologic therapies are available to treat the symptoms of autonomic neuropathy.

■ MANIFESTATIONS ARE VARIED AND SERIOUS

Neuropathy is one of the most common complications of diabetes. When it affects the autonomic nervous system, it can damage the cardiovascular, gastrointestinal, and genitourinary systems and impair metabolic functions such as glucose counterregulation (FIGURE 1). Diabetic autonomic neuropathy impairs the ability to conduct activities of daily living, lowers quality of life, and increases the risk of death. It also accounts for a large portion of the cost of care.²

The autonomic nervous system is primarily efferent, transmitting impulses from the central nervous system to peripheral organs. However, it also has an afferent component. Its two divisions—the parasympathetic and the sympathetic nervous systems—work in



balanced opposition to control the heart rate, the force of cardiac contraction, the dilatation and constriction of blood vessels, the contraction and relaxation of smooth muscle in the digestive and urogenital systems, the secretions of glands, and pupillary size.

Diabetes can cause dysfunction of any or every part of the autonomic nervous system, leading to a wide range of disorders. And these are serious: among the most troublesome and dangerous of the conditions linked to autonomic neuropathy are known or silent myocardial infarction (MI), cardiac arrhythmias, ulceration, gangrene, and nephropathy. Autonomic neuropathy is also associated with an increased risk of sudden death.

■ NEUROPATHY IS COMMON AND BEGINS EARLY

The reported prevalence of diabetic autonomic neuropathy varies, with community-based studies finding lower rates than clinic-based and hospital-based studies, in which the prevalence may be as high as 100%.³

Clinical symptoms generally do not develop for many years after the onset of diabetes. However, subclinical autonomic neuropathy can often be identified by quantitative functional testing within 1 year of diagnosis in patients with type 2 diabetes and within 2 years in those with type 1 diabetes.⁴

The most important causative factors are poor glycemic control, long duration of diabetes, increasing age, female sex, and higher body mass index.

■ MORTALITY IS HIGH

Of patients with symptomatic autonomic dysfunction, 25% to 50% die within 5 to 10 years of diagnosis.^{5,6} The 5-year mortality rate in patients with diabetic autonomic neuropathy is three times higher than in diabetic patients without autonomic involvement.⁷

Leading causes of death in diabetic patients with either symptomatic or asymptomatic autonomic neuropathy are heart disease and nephropathy. Increased urinary albumin excretion is related to autonomic neuropathy in diabetic patients.^{8,9} Impairments in the autonomic nervous system may also con-

tribute to the pathogenesis of diabetic nephropathy and cardiovascular disease. Autonomic neuropathy is also an independent risk factor for stroke.¹⁰

■ A DIAGNOSIS OF EXCLUSION

The diagnosis of diabetic autonomic neuropathy is one of exclusion, and many other causes of autonomic dysfunction should first be ruled out (TABLE 1). The clinician should take a careful history, asking about diabetes, cancer, drug use, alcohol use, HIV exposure, and family history of familial amyloidosis.

Patients should be asked whether they have traveled to South America, where they might have been exposed to *Trypanosoma cruzi*, the cause of Chagas disease. Serologic testing for antibodies to this organism may be valuable.

Testing the norepinephrine response to standing may help identify the cause of idiopathic orthostatic hypotension. Basal values and the response to standing are normal in diabetic autonomic neuropathy, severely reduced in multiple system atrophy or idiopathic orthostatic hypotension, and impaired in Shy-Drager syndrome.

■ GLYCEMIC CONTROL IS IMPORTANT

For patients with either type 1 or type 2 diabetes, glycemic control is important, although methods to achieve target levels may differ. The methods for achieving euglycemia and the target blood glucose and hemoglobin A_{1c} levels are given in a position statement from the American Diabetes Association available online at www.diabetes.org/clinicalrecommendations/CareSup1Jan01.htm and in supplement 1 of *Diabetes Care* 2001, volume 24.

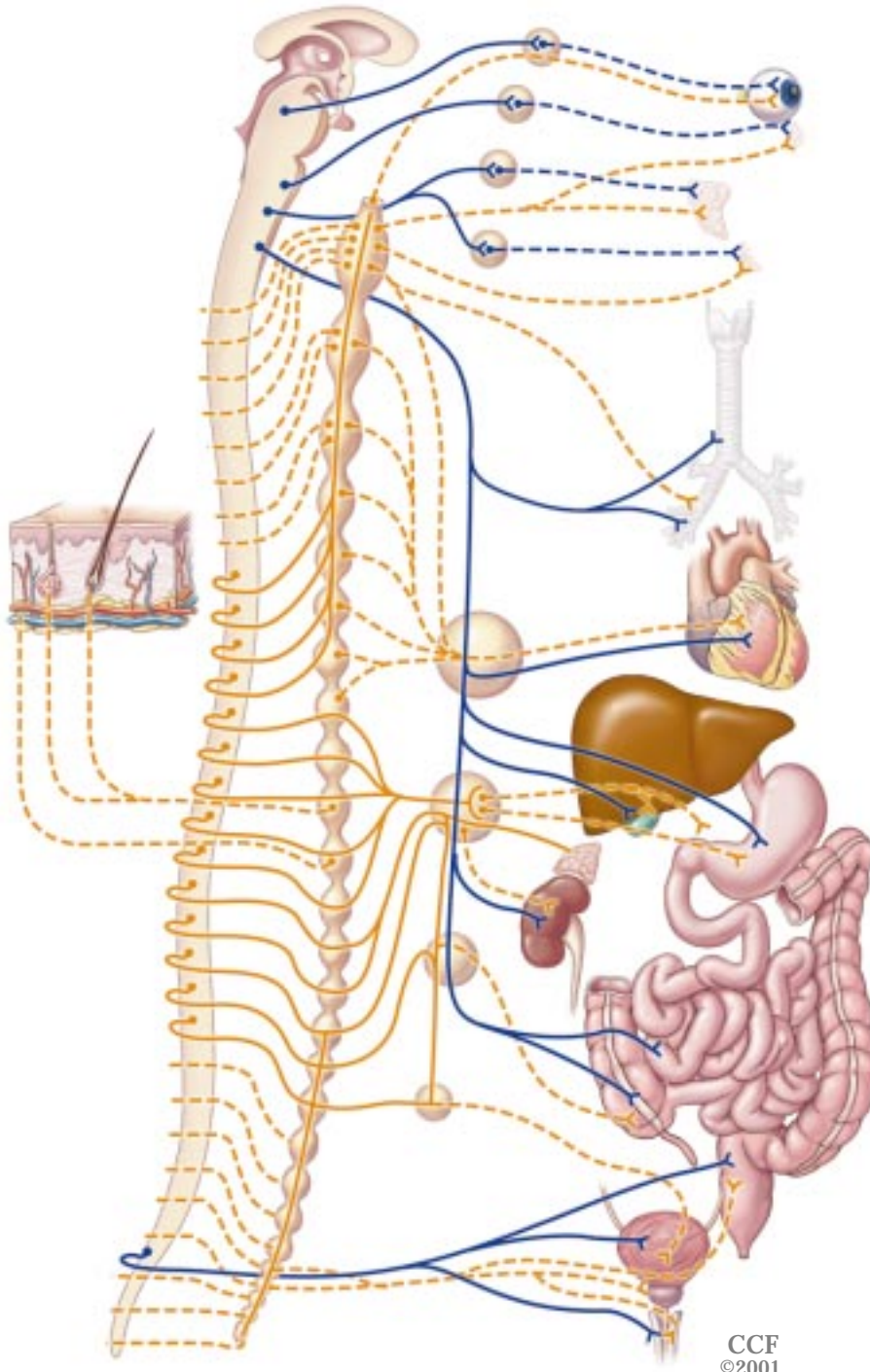
■ CARDIOVASCULAR AUTONOMIC NEUROPATHY

Cardiovascular autonomic neuropathy causes abnormalities of heart-rate control and vascular dynamics.¹¹ It has been linked to postural hypotension, exercise intolerance, enhanced intraoperative cardiovascular lability, increased incidence of asymptomatic ischemia, myocardial infarction, and decreased likelihood of survival after myocardial infarction.¹²⁻¹⁵

First, rule out other causes of autonomic dysfunction

Clinical manifestations of autonomic neuropathy

Diabetes can cause dysfunction of any or all parts of the autonomic nervous system, leading to a wide range of disorders. (Sympathetic fibers are shown in orange, parasympathetic in blue, preganglionic solid, and postganglionic dashed.)



Pupillary

Decreased diameter of dark-adapted pupil
Argyll-Robertson type pupil

Metabolic

Hypoglycemia unawareness
Hypoglycemia unresponsiveness

Cardiovascular

Tachycardia, exercise intolerance
Cardiac denervation
Orthostatic hypotension
Heat intolerance

Neurovascular

Areas of symmetrical anhidrosis
Gustatory sweating
Hyperhidrosis
Alterations in skin blood flow

Gastrointestinal

Constipation
Gastroparesis diabeticorum
Diarrhea and fecal incontinence
Esophageal dysfunction

Genitourinary

Erectile dysfunction
Retrograde ejaculation
Cystopathy
Neurogenic bladder
Defective vaginal lubrication

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FIGURE 2

TABLE 1

Differential diagnosis of diabetic autonomic neuropathy

Idiopathic orthostatic hypotension
Shy-Drager syndrome (orthostatic hypotension, pyramidal and cerebral signs including tremor, rigidity, hyperreflexia, ataxia, and urinary and bowel dysfunction)
Panhypopituitarism
Pheochromocytoma
Chagas disease
Amyloidosis
Hypovolemia caused by poor glycemic control or diuretics
Effects of insulin
Complications from vasodilators (nitrates, calcium channel blockers, hydralazine)
Complications from sympathetic blockers (methyldopa, clonidine, prazosin, guanethidine, phenothiazine, tricyclic antidepressants)
Orthostatic hypotension caused by alcoholic neuropathy
Congestive heart failure
Other causes of diarrhea, constipation, and gastrointestinal dysfunction
Other causes of genitourinary and erectile dysfunction
Other causes of pedal edema
Hypoglycemia unresponsiveness and unawareness occurring with intensive glycemic control
The Argyll-Robertson pupil of syphilis

**Resting
tachycardia
is an early sign
of autonomic
neuropathy**

Cardiovascular autonomic neuropathy occurs in about 17% of patients with type 1 diabetes and 22% of those with type 2. An additional 9% of type 1 patients and 12% of type 2 patients have borderline dysfunction.¹⁶

The medical consequences of cardiovascular autonomic neuropathy in diabetes are dramatic: a meta-analysis of 11 studies concluded that the 5.5-year mortality rate was 5% among patients with diabetes with normal heart-rate variability vs 27% among those with abnormal heart-rate variability.¹⁷

Cardiovascular symptoms and signs

Lack of heart-rate variability during deep breathing or exercise is a sign of autonomic neuropathy and is associated with a high risk of coronary heart disease in patients with or without diabetes.¹⁸ The Diabetes Control and Complications Trial (DCCT) found that 1.6% of patients with a 5-year history of diabetes had this sign. The rate rose to 6.2% of those with a 5-year to 9-year history of diabetes, and to 12% in those who had had the disease for more than 9 years.¹⁹

Resting tachycardia is an early sign, as is loss of heart-rate variation during deep breathing,²⁰ whereas a heart rate that does not

respond to mild exercise indicates nearly complete cardiac denervation.

Limited exercise tolerance is due to impaired sympathetic and parasympathetic responses that normally augment cardiac output and redirect peripheral blood flow to skeletal muscles. Exercise tolerance is also reduced by a reduced ejection fraction, systolic dysfunction, and decreased diastolic filling.

A prolonged corrected QT interval (QTc) indicates an imbalance between right and left sympathetic innervation.²¹ Diabetic patients with a regional sympathetic imbalance and QTc interval prolongation may be at greater risk for arrhythmias.

Abnormal circadian pattern of blood pressure. In this condition, blood pressure rises during the night and falls in the early morning. This abnormal pattern has been shown to correlate with postural hypotension due to cardiovascular autonomic neuropathy.²²

Blunted symptoms of coronary artery disease. Diabetic patients have a high rate of coronary artery disease, which may be asymptomatic owing to subclinical neuropathy.^{23,24} Indeed, painless ischemia is significantly more frequent in patients with autonomic neuropathy than in those without it (38% vs 5%). The lack of pain

TABLE 2

Diagnostic tests for cardiovascular autonomic neuropathy**Resting heart rate**

> 100 beats/minute is abnormal

Beat-to-beat heart rate variation

The patient should abstain from drinking coffee overnight

Test should not be performed after overnight hypoglycemic episodes

When the patient lies supine and breathes 6 times per minute, a difference in heart rate of less than 10 beats/minute is abnormal

An expiration:inspiration R-R ratio > 1.17 is abnormal

Heart rate response to standing

The R-R interval is measured at beats 15 and 30 after the patient stands

A 30:15 ratio of less than 1.03 is abnormal

Heart rate response to Valsalva maneuver

The patient forcibly exhales into the mouthpiece of a manometer, exerting a pressure of 40 mm Hg for 15 seconds

A ratio of longest to shortest R-R interval of less than 1.2 is abnormal

Systolic blood pressure response to standing

Systolic blood pressure is measured when the patient is lying down and 2 minutes after the patient stands

A fall of more than 30 mm Hg is abnormal

A fall of 10 to 29 mm Hg is borderline

Diastolic blood pressure response to isometric exercise

The patient squeezes a handgrip dynamometer to establish his or her maximum

The patient then squeezes the grip at 30% maximum for 5 minutes

A rise of less than 16 mm Hg in the contralateral arm is abnormal

Electrocardiography

A QTc of more than 440 ms is abnormal

Depressed very-low frequency peak or low-frequency peak indicate sympathetic dysfunction

Depressed high-frequency peak indicates parasympathetic dysfunction

Lowered low-frequency/high-frequency ratio indicates sympathetic imbalance

Neurovascular flow

Noninvasive laser Doppler measures of peripheral sympathetic responses to nociception

**Painless MI
is particularly
common**

is the result of damaged afferent nerves. In the Framingham study, 39% of patients with diabetes had had an asymptomatic MI documented by electrocardiography.¹⁵

Silent ischemia and silent MI are particularly dangerous because patients cannot sense the pain and seek help.²⁵ One study²⁶ found a mortality rate after asymptomatic MI of 47%, whereas mortality after MI with pain was 35%.²⁶

In nondiabetic patients, the risk of acute MI is highest in the morning. This diurnal variation is altered in diabetic patients, who have a lower morning peak and a higher frequency of infarctions during the evening. The blunting in the morning peak is the result of

altered sympathovagal balance and reduced nocturnal vagal activity in patients with cardiac autonomic neuropathy.^{27,28}

Pain in any part of the chest in a patient with diabetes should be considered of myocardial origin until proven otherwise. Other clues to a possible silent MI include unexplained fatigue, confusion, edema, hemoptysis, nausea and vomiting, diaphoresis, arrhythmias, cough, and dyspnea.

**Cardiac functional testing
of the autonomic nervous system**

Tests of cardiovascular reflexes are sensitive, reproducible, simple, and noninvasive and allow extensive evaluation of diabetic cardio-



vascular autonomic neuropathy. These include measurements of the resting heart rate, beat-to-beat heart-rate variation, blood pressure response to the Valsalva maneuver, heart rate and systolic blood pressure response to standing, diastolic blood pressure response to sustained exercise, and the QT interval (TABLE 2).

An increased resting heart rate and loss of heart-rate variation in response to deep breathing are primary indicators of parasympathetic dysfunction. Tests for sympathetic dysfunction include measurements of heart rate and blood pressure responses to standing, exercise, and handgrip.

Reduced 24-hour heart-rate variability, a newer test, is believed to be more sensitive than standard reflex tests and can detect cardiac autonomic dysfunction earlier.²⁹ A 24-hour recording of heart-rate variability can reveal abnormal circadian rhythms regulated by sympathovagal activity. In vagal dysfunction, the high-frequency component of heart rate variability is reduced; in sympathetic dysfunction, the low-frequency and very low-frequency components are reduced. Furthermore, in advanced cardiac autonomic neuropathy all three components are reduced, as is the low-frequency:high-frequency ratio, which represents sympathovagal balance.³⁰

Heart rate variability should be assessed during deep breathing (to calculate the expiration:inspiration ratio), the Valsalva maneuver, and standing. Abnormalities in two or more of these tests suggest a diagnosis of autonomic neuropathy. Patients with type 1 diabetes should be tested 5 years after diagnosis and yearly thereafter; patients with type 2 diabetes should be tested at diagnosis and yearly thereafter (TABLE 3).

Nuclear imaging

The sympathetic innervation of the heart can be visualized and quantified by single-photon emission computed tomography with iodine 123 metaiodobenzylguanidine (MIBG).

Treating cardiac manifestations of diabetic autonomic neuropathy

Intensive glycemic control is critical to preventing the onset of diabetic autonomic neuropathy and slowing its progression.

TABLE 3

Screening for and treating diabetic autonomic neuropathy**1. TIGHT GLYCEMIC CONTROL**

For all diabetic patients: maintain aggressive control of blood glucose, hemoglobin A_{1c}, blood pressure, and lipids with pharmacologic therapy and lifestyle changes

2. SCREENING**Begin screening**

5 years after diagnosis of type 1 diabetes

At the time of diagnosis of type 2 diabetes

Ask about symptoms**Examine for signs****Test for heart-rate variability**

Expiration:inspiration ratio

Response to Valsalva maneuver

Response to standing

If negative: repeat yearly

If positive: apply appropriate diagnostic tests, treat symptoms

3. TREATMENT

SYMPTOMS	TESTS	TREATMENTS
Cardiac	Multigated angiography (MUGA) Thallium scan ¹²³ I metaiodobenzylguanidine (MIBG) scan	ACE inhibitors Beta-blockers Antioxidants Aldose reductase inhibitors
Postural hypotension	Measure blood pressure standing and supine Measure catecholamines	Supportive garments Clonidine Midodrine Octreotide
Gastrointestinal	Emptying study Barium study Endoscopy Manometry Electrogastrogram	Prokinetic agents Antibiotics Bulking agents Tricyclic antidepressants Pancreatic extracts
Sexual dysfunction	Penile-brachial pressure index Nocturnal penile tumescence	Sex therapy Psychological counseling Sildenafil Prostaglandin E ₁ injection Device or prosthesis
Bladder dysfunction	Cystometrogram Postvoiding sonography	Bethanechol Intermittent catheterization
Sudomotor (sweating) dysfunction	Quantitative sudomotor axon reflex Sweat test Skin blood flow	Scopolamine Glycopyrrrolate Botulinum toxin Vasodilators

4. FOLLOW-UP

Monitor every year for response to treatment

Orthostatic hypotension is often incorrectly ascribed to hypoglycemia

Intensive glycemic control substantially reduces the prevalence of autonomic dysfunction² and slows the deterioration of R-R variation and Valsalva ratio.³¹

Intensive glycemic control can reverse

deterioration in heart-rate variability in as little as 1 year of therapy.³² However, the response to improved glycemic control depends on the degree of autonomic dysfunction at baseline.



In a study of diabetic patients with microalbuminuria,³³ the stepwise implementation of intensified multifactorial treatment slowed the progression to autonomic neuropathy. Reduced heart-rate variation was used to select high-risk diabetic patients who required aggressive interventions with beta-blockers. ACE inhibition increased heart-rate variation and decreased mortality in patients with mild microalbuminuria.

Beta-blockers that are cardioselective (eg, atenolol, metoprolol, acebutolol) or lipophilic (eg, propranolol, metoprolol) might modulate the effects of autonomic dysfunction in diabetes either centrally or peripherally by opposing the sympathetic stimulus, and thereby restore the parasympathetic-sympathetic balance.³⁴

Alpha-lipoic acid was shown in multicenter clinical trials³⁵ to slow or reverse the progression of cardiovascular autonomic neuropathy if started early in the disease. The results of multicenter trials of alpha-lipoic acid should be available in 2002.

Aldose reductase inhibitors may also reverse the progression of diabetic autonomic neuropathy.³⁶ These drugs reduce the flux of glucose through the polyol pathway, inhibiting tissue accumulation of sorbitol and fructose. However, they are not currently approved for clinical use in the United States; the only patients receiving them are participants in clinical trials.

■ ORTHOSTATIC HYPOTENSION

Orthostatic hypotension, another sign of autonomic neuropathy, is a fall in systolic blood pressure of more than 30 mm Hg upon standing. The cause is damaged vasoconstrictor fibers, impaired baroreceptor function, and poor cardiovascular reactivity. Orthostatic hypotension may be accompanied by dizziness, weakness, faintness, visual impairment, pain in the back of the head, and loss of consciousness.

Two pathophysiologic states cause orthostatic hypotension: autonomic insufficiency and intravascular volume depletion. A physical examination and history should easily rule out volume depletion.

Factors that may aggravate orthostatic hypotension in diabetic autonomic neuropathy and should be looked for include volume

depletion due to diuretics, excessive sweating, diarrhea, or polyuria. Medications that may contribute to the problem include antihypertensives, beta-blockers (which impair heart rate responses), and tricyclic antidepressants and phenothiazines (which impair vasoconstriction by blocking adrenergic action).

Many people with this condition abruptly become hypotensive when eating or within 10 to 15 minutes of an insulin injection. The symptoms are similar to those of hypoglycemia (though they occur earlier) and are often incorrectly ascribed to the hypoglycemic action of insulin.

Insulin may mediate the hypotension by increasing capillary permeability, causing a mild intravascular depletion. Insulin may also directly stimulate endothelial release of nitric oxide, a potent vasodilator, and sensitize smooth muscle to the relaxant effects of prostacyclin and nitric oxide, thereby causing vasodilation unopposed by the action of norepinephrine.³⁷ Impaired vagal heart rate control and sympathetic nervous dysfunction, which occur with advanced autonomic neuropathy, exaggerate the hemodynamic effects of insulin and worsen insulin-induced hypotension.³⁸

Treating orthostatic hypotension

Orthostatic hypotension is difficult to manage, because the standing blood pressure must be raised without causing hypertension when the patient lies down.

Nonpharmacologic therapy should be tried first. Patients should be advised to wear supportive stockings to increase venous return, removing them at bedtime. They should be cautioned to get out of bed slowly, to avoid hot baths, and to take their insulin injections while lying down.

9-fluorohydrocortisone and supplementary salt may benefit some patients with orthostatic hypotension. Unfortunately, these agents do not improve symptoms until edema develops, which carries a risk of causing congestive heart failure and hypertension.

Clonidine, an alpha-2 agonist, can treat a deficiency of alpha-2 adrenergic receptor. However, in some patients with diabetic orthostatic hypotension, clonidine can actually increase blood pressure. The initial dose

Tight glycemic control is critical in preventing diabetic autonomic neuropathy

TABLE 4

Pharmacologic therapies for diabetic autonomic neuropathy

INDICATION	DRUG AND DOSAGE	SIDE EFFECTS
Orthostatic hypotension	9-Alpha fluorohydrocortisone 0.5–2 mg/day Clonidine 0.1–0.5 mg at bedtime Octreotide 0.1–0.5 µg/kg/day	Congestive heart failure, hypertension Hypotension, sedation, dry mouth Injection site pain, diarrhea
Gastroparesis	Metoclopramide 10 mg 30–60 minutes before meals and at bedtime Domperidone 10–20 mg 30–60 minutes before meals and at bedtime Erythromycin 250 mg 30 minutes before meals Levosulpiride 25 mg three times a day	Galactorrhea, extrapyramidal symptoms Galactorrhea Abdominal cramps, nausea, diarrhea, rash Galactorrhea
Diarrhea	Metronidazole 250 mg three times a day for at least 3 weeks Clonidine 0.1 mg two or three times a day Cholestyramine 4 g one to six times a day Loperamide 2 mg four times a day Octreotide 50 µg three times a day	Orthostatic hypotension Toxic megacolon Aggravation of nutrient malabsorption
Cystopathy	Bethanechol 10 mg four times a day Doxazosin 1–2 mg two or three times a day	Hypotension, headache, palpitations
Erectile dysfunction	Sildenafil 50 mg 1 hour before sexual activity, once only per day	Headache, flushing, nasal congestion, dyspepsia, musculoskeletal pain, blurred vision; interacts with nitrate-containing drugs (hypotension and fatal cardiac events)

should therefore be small and increased gradually.

Midocrine, an alpha-1 adrenergic agonist, might be of benefit if nonpharmacologic measures, cortisone, salt supplementation, and clonidine fail.

Octreotide may help some patients who experience particularly refractory orthostatic hypotension after eating (TABLE 4).

■ ALTERATIONS IN SKIN BLOOD FLOW

Microvascular skin flow is regulated by both the central and peripheral components of the autonomic nervous system and can thus be deranged by diabetic autonomic neuropathy.

This derangement can disrupt the maintenance of regional and whole-body temperature through the apical or glabrous skin, which is the smooth skin on the palm of the hand, the sole of the foot, and the face. Apical skin contains a large number of arteriovenous anastomoses or shunts for thermoregulation.

A disruption to the blood supply can also

interfere with nutrient supply to the skin on the rest of the body, which is called nonapical or hairy skin. In hairy skin, functional defects in small capillary circulation can be identified before neuropathy develops.^{39–41} The result is dry skin, impaired sweating, and the development of fissures and cracks that are portals for microorganisms that cause infectious ulcers and gangrene.

Microvascular blood flow can be measured noninvasively using laser Doppler flowmetry under basal and stimulated conditions.

Use of emollients can soften skin and prevent dryness and cracking, reducing entry of microorganisms that cause infection, ulceration, and gangrene.

■ GASTROINTESTINAL AUTONOMIC NEUROPATHY

Gastrointestinal disturbances caused by autonomic neuropathy are common. Some are disabling, but many are mild. Gastrointestinal



disturbances are often overlooked and untreated.^{42,43} They appear to be more common in patients with long-standing disease and poorly controlled blood glucose levels.

These conditions may affect any part of the gastrointestinal tract. The most prevalent complications are motility disturbances of the viscera, which are generally the result of widespread autonomic neuropathy. They include dysphagia, abdominal pain, nausea, vomiting, malabsorption, fecal incontinence, diarrhea, and constipation.⁴⁴

Constipation

Constipation is the most common gastrointestinal complication, affecting nearly 60% of diabetic patients. It may be associated with atony of the large bowel and rectum and sometimes with megacolon. Bouts of constipation may alternate with episodes of diarrhea.⁴⁵

Evaluating constipation. Before attributing constipation to diabetic autonomic neuropathy, the clinician should rule out other causes such as hypothyroidism, side effects of drugs such as amitriptyline or calcium channel blockers, and colonic carcinoma. All patients should have a careful digital rectal examination, and women should have a bimanual pelvic examination. Three stool specimens should be tested for occult blood. Anorectal manometry may be used to assess the rectal anal inhibitory reflex, which can distinguish rectosigmoid dysfunction and outlet-obstructive symptoms from colonic hypomotility.

Treatment for constipation should begin with emphasis on good bowel habits, which include regular exercise and maintenance of adequate hydration and fiber consumption. Sorbitol and lactulose may be helpful. The intermittent use of saline or osmotic laxatives may be required for patients with more severe symptoms.

Gastric dysfunction

Diabetic autonomic neuropathy can impair both gastric acid secretion and gastrointestinal motility, causing gastroparesis diabeticorum, which can be detected in 25% of patients with diabetes. It is most often clinically silent, but the severe form is one of the most debilitating gastrointestinal complications of diabetes.

The typical symptoms of diabetic gastroparesis are early satiety, nausea, vomiting, abdominal bloating, epigastric pain, and anorexia. Patients with gastroparesis have emesis of undigested food consumed many hours or even days previously. Episodes of nausea and vomiting may last days to months, or they may occur in cycles.⁴⁶

Upper gastrointestinal symptoms should not be attributed to gastroparesis until conditions such as gastric ulcer, duodenal ulcer, gastritis, and gastric cancer have been excluded. However, gastroparesis should always be suspected in patients with erratic glucose control. Even when mild, gastroparesis interferes with nutrient delivery to the small bowel and therefore disrupts the relationship between glucose absorption and exogenous insulin administration. This may result in wide swings of glucose levels, unexpected episodes of postprandial hypoglycemia, and apparent "brittle diabetes."

Evaluating gastric dysfunction. Gastric emptying can be visualized by scintigraphic imaging after the patient consumes radionuclide-labeled food, but the scintigraphic results do not always correlate with the severity of the symptoms. Some diabetic patients with delayed gastric emptying may have no symptoms, and others with apparently normal emptying may have severe symptoms.

Gastroduodenal manometry may be helpful in patients with symptoms but apparently normal emptying because it can help identify pylorospasm or incoordinate gastric and duodenal motility. Magnetic resonance imaging and percutaneous electrogastrography hold promise for future clinical application. However, manometric studies and electrogastrography are generally available only in research settings.

Treating diabetic gastroparesis. Initial treatment of diabetic gastroparesis should focus on blood glucose control, which improves gastric motor function. In addition, patients should be advised to eat multiple small meals (4–6 per day) and to reduce the fat content of their diet to less than 40 g/day. They should also restrict their fiber intake to prevent the formation of bezoars.⁴⁷

Prokinetic agents used to treat diabetic gastropathy are metoclopramide, domperi-

Suspect
gastroparesis if
glucose control
is erratic

done, erythromycin, and levosulpiride (TABLE 4).^{48,49} Unfortunately, after the first few doses, tachyphylaxis develops and these agents become progressively less effective. Periodic withdrawal restores responsiveness and should be tried in apparently refractory cases. In severe cases, jejunostomy may allow the stomach to rest until it recovers its function.

Diabetic diarrhea

Diarrhea affects 20% of diabetic patients and is more frequent in those with known autonomic neuropathy. A characteristic symptom of diabetic diarrhea is an intermittent pattern of episodes lasting from several hours to several days. Nocturnal diarrhea and fecal incontinence are common. The patient may have as many as 20 to 30 bowel movements in 24 hours. Diarrhea may result from intestinal hypermotility caused by diminished sympathetic inhibition, hypomotility with bacterial overgrowth, pancreatic insufficiency, steatorrhea, or bile-salt malabsorption.⁵⁰

Evaluating diabetic diarrhea. Drug-related diarrhea from agents such as metformin and acarbose should be excluded, as should lactose intolerance. Diarrhea that resolves with fasting may be osmotic, caused by ingested substances. In contrast, diarrhea that continues when the patient is not eating, such as nocturnal diarrhea, suggests that the cause is a secretory process, and neuroendocrine causes should be pursued.

Common causes of these endocrine diarrhea syndromes are carcinoid tumors, carcinoid syndrome, calcitonin-secreting tumors, PPomas (pancreatic polypeptide-secreting tumors), somatostatinomas, VIPomas (vasoactive intestinal polypeptide-secreting tumors), and gastrinomas. Measurement of the fasting concentrations of hormones in serum and the urinary excretion of 5HIAA (5-hydroxyindoleacetic acid) and the foregut carcinoid markers substance P and CGRP (calcitonin gene-related peptide) will usually identify the cause.

Treating diabetic diarrhea. Initial therapy of diabetic diarrhea should be directed toward correcting fluid and electrolyte disturbances and improving nutrition. As with all types of diabetic autonomic dysfunction, good control of glucose levels is also helpful.

Treatment should be directed at the iden-

tified cause of diabetic diarrhea. Antidiarrheal agents (eg, loperamide and diphenoxylate) can reduce the number of stools, but they may also be associated with toxic megacolon and so should be used with extreme care (TABLE 4). A broad-spectrum antibiotic such as doxycycline or metronidazole is usually the treatment of choice for bacterial overgrowth. Chelation of bile salts may relieve symptoms.

Clonidine may reverse adrenergic nerve dysfunction and improve diarrhea. This agent clearly reduces volume of stool in severe cases but does not stop diarrhea. High doses of clonidine may be required for diarrhea of diabetic enteropathy. Diarrhea resistant to treatment with these agents will respond to octreotide (TABLE 4).

Esophageal dysfunction

Esophageal motility disorders such as dysphagia, retrosternal discomfort, and heartburn are uncommon in diabetes.⁵¹ Esophageal dysfunction is detectable through esophageal motility tests and scintigraphy. Clinicians should monitor patients who use drugs associated with esophageal erosion and perforation, such as the oral bisphosphonates.

■ GENITOURINARY TRACT DISTURBANCES

Diabetic autonomic neuropathy can be associated with voiding dysfunction or erectile problems. The latter condition is particularly important because it may signal cardiovascular problems.

Erectile dysfunction

The prevalence of erectile or sexual dysfunction is about 50% in men with diabetes and about 30% in women, but limitations in assessing female sexual dysfunction may be the reason for the apparent sex-related difference. Erectile dysfunction may be the presenting symptom of diabetes, and more than 50% of men with diabetes notice the onset of erectile dysfunction within 10 years of onset of the diabetes.^{48,52}

In men, neuropathy can cause loss of penile erection, retrograde ejaculation, or both, without affecting libido, potency, or orgasmic function. Early symptoms include decreased rigidity and incomplete tumes-

Erectile
dysfunction is a
coronary
disease marker



cence. Morning erections are lost, and impotence progresses gradually over a period of 6 months to 2 years. In contrast, a sudden loss of erections with a particular partner, without an accompanying loss of morning erections or nocturnal penile tumescence, suggests a psychological cause. However, psychogenic factors may be superimposed on organic dysfunction in diabetes.

Importantly, erectile dysfunction is a marker for the development of generalized vascular disease and for premature death from MI. It may also presage future cardiovascular events. Thus, physicians should perform cardiovascular evaluations in all diabetic patients with erectile dysfunction.

Erectile dysfunction is multifactorial. In addition to neuropathy, contributing factors include vascular disease, metabolic control, nutritional deficiencies, endocrine disorders, psychogenic factors, and drugs used in the treatment of diabetes and its complications. Autonomic neuropathy contributes by impeding cholinergic activation of the erectile process, through which, in healthy people, acetylcholine acts upon the vascular endothelium to release nitric oxide and prostacyclin. There is also evidence that non-adrenergic/noncholinergic nerve function is hampered by decreased levels of VIP (vasoactive intestinal peptide), substance P, and other vasodilatory neurotransmitters.

Evaluating erectile dysfunction. A thorough workup for impotence in men should include a medical and sexual history, physical and psychological evaluations, a blood test for diabetes, assays for testosterone, prolactin, and thyroid hormones, a test for nocturnal erections, tests to assess penile, pelvic, and spinal nerve function, and assessments of penile blood supply and blood pressure.

Physical examination must include an evaluation of the autonomic nervous system, vascular supply, and hypothalamic-pituitary-gonadal axis. Autonomic neuropathy that causes erectile dysfunction is almost always accompanied by loss of the ankle jerk reflex and absent or reduced vibration sense over the large toes. To determine the integrity of sacral parasympathetic divisions, the physician should assess perianal sensation, sphincter tone, and the bulbocavernosus reflex.

TABLE 5

Drugs known to cause erectile dysfunction that are used by diabetic patients

Antihypertensive agents

Beta-blockers
Thiazide diuretics
Spironolactone
Methyldopa
Reserpine

Agents acting on the central nervous system

Phenothiazines
Haloperidol
Tricyclic antidepressants

Drugs acting on the endocrine system

Estrogens
Antiandrogens
Gonadotropin antagonists
Spironolactone
Cimetidine
Metoclopramide
Fibric acid derivatives
Alcohol
Marijuana

Stenosis of the internal pudendal artery is another potential cause of impotence. A penile/brachial index of less than 0.7 indicates diminished blood supply. A venous leak manifests as unresponsiveness to vasodilators and must be evaluated by penile Doppler sonography.

To distinguish psychogenic from organic erectile dysfunction, nocturnal penile tumescence may be assessed. Patients with normal nocturnal penile tumescence are considered to have psychogenic erectile dysfunction.

Treating erectile dysfunction. Initially, the patient should be urged to forego alcoholic drinks and smoking, cease taking medications known to cause erectile dysfunction (TABLE 5), and optimize metabolic glucose control.

Sildenafil (Viagra) may be taken at a dose of 50 mg, or lower for patients with renal failure or hepatic dysfunction. It is not recommended for patients with ischemic heart disease and is absolutely contraindicated in patients being treated with nitroglycerine or other nitrate-containing drugs.⁵³

Sildenafil is contraindicated in those receiving nitrates

For many men, direct injection of prostacyclin into the corpus cavernosum will produce satisfactory erections. Surgically implanted penile prostheses are also available.

Retrograde ejaculation

Retrograde ejaculation is caused by damage to efferent sympathetic nerves that coordinate the simultaneous closure of the internal vesicle sphincter and relaxation of the external vesicle sphincter during ejaculation. Absence of spermatozoa in the semen and presence of motile sperm in a postcoital specimen of urine confirm the diagnosis. Clinically, retrograde ejaculation is of little significance unless it prevents a patient from fathering children. In that case, the patient needs to pursue assisted reproduction whereby the sperm are retrieved from the bladder for artificial insemination.

Female sexual dysfunction

Women may experience decreased sexual arousal or inadequate lubrication and pain during sexual intercourse.⁵⁴

There are no guidelines for diagnosing female sexual dysfunction, as there are for diagnosing erectile dysfunction. Some researchers have used vaginal plethysmography to measure lubrication and vaginal flushing, but the technique is not well established.

Treatment usually requires application of vaginal lubricants, including topical estrogen creams. Current studies are being done on transdermal sildenafil to enhance blood flow.

Cystopathy

In diabetic autonomic neuropathy, the motor function of the bladder is unimpaired, but damage to the afferent fibers diminishes bladder sensation. The bladder can become enlarged to more than three times its normal size, but the loss of sensation means that the distention causes no discomfort. Voiding frequency is diminished, and the patient is no longer able to void completely. Dribbling and overflow incontinence are common effects. A postvoiding residual volume of more than 150 mL is diagnostic of cystopathy. Cystopathy may put the patients at risk for urinary infections.⁵⁵

Treating cystopathy. Patients with cystopathy should be instructed to palpate their bladder and to try to urinate when it is

full. If they are unable to start urination, they should massage or press the abdomen just above the pubic bone (the Credé maneuver) to start the flow of urine.

Pharmacotherapy should be directed at improving bladder emptying and reducing the risk of urinary tract infection. Parasympathomimetics such as bethanechol are sometimes helpful, although frequently they do not fully empty the bladder. Extended sphincter relaxation can be achieved with an alpha-1 blocker, such as doxazosin (TABLE 4).

Self-catheterization can be particularly useful and has a low risk of infection.

■ SWEATING DISTURBANCES

Hyperhidrosis of the upper body and anhidrosis of the lower body are characteristic features of autonomic neuropathy. Hyperhidrosis associated with eating, known as gustatory sweating, may be linked with certain foods, particularly spicy foods and cheeses. Patients can get relief by avoiding the inciting food.

The loss of lower body sweating can cause dry, brittle skin that cracks easily, predisposing the patient to ulcer formation that can lead to loss of the limb. For such patients, special attention must be paid to foot care.

Glycopyrrolate (an antimuscarinic compound) may benefit diabetic patients with gustatory sweating.⁵⁶

■ METABOLIC DYSFUNCTION: LACK OF AWARENESS AND RESPONSE TO HYPOGLYCEMIA

Unawareness of hypoglycemia and unresponsiveness to it are serious problems that hamper the patient's ability to manage his or her diabetes. Both are caused by impairments of the sympathetic and parasympathetic nervous system.

In most diabetic patients, catecholamine release, triggered by low glucose levels, produces noticeable symptoms such as tremulousness and cold sweat, which alert the patient to eat and take other measures to prevent coma. Diabetic autonomic neuropathy impairs catecholamine release and prevents the warning signs of hypoglycemia, leaving the patient unaware of it.

Consider less
intense glucose
control if
hypoglycemia
unawareness is
present



The related problem of glycemic unresponsiveness to hypoglycemia occurs when impaired autonomic responses derange glucose counterregulation during fasting or periods of increased insulin activity. In healthy people and in patients with early-stage diabetes, these autonomic responses result in the release of glucagon and epinephrine for short-term glucose counterregulation, and of growth hormone and cortisol for long-term regulation. Failure in glucose counterregulation can be confirmed by the absence of glucagon and epinephrine responses to hypoglycemia induced by a controlled dose of insulin.⁵⁷

The glucagon response becomes impaired after 1 to 5 years of type 1 diabetes. After 14 to 31 years, the glucagon response is almost undetectable, and it is absent in patients with autonomic neuropathy.

Treating hypoglycemia unawareness and unresponsiveness

These conditions are difficult to manage. Although normalized glucose level is usually the goal of treatment for diabetic patients, it should not be the goal for those with hypo-

glycemic unawareness and unresponsiveness.⁵⁸ In such patients, lowered glucose levels increase the risk of hypoglycemia, and their unawareness and inability to mount a counterregulatory response makes hypoglycemia especially dangerous.

For patients using an insulin pump, we therefore recommend using boluses of less than the calculated amount. In intensive glycemic control therapy, we recommend using very small boluses of long-acting insulin.

Unfortunately, intensive insulin treatment may produce a functional autonomic insufficiency that is virtually identical to autonomic neuropathy. In patients with this problem, as for patients with bona fide autonomic neuropathy and hypoglycemic unresponsiveness, therapy should be relaxed so that glucose levels can rise. If hypoglycemia occurs in these patients at a certain glucose level, it will take a lower glucose level to trigger the same symptoms in the next 24 to 48 hours. Avoiding hypoglycemia for a few days will allow the adrenergic response to recover.



REFERENCES

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive diabetes therapy on the development and progression of neuropathy. *Ann Intern Med* 1995; 122:561–568.
2. Vinik AI, Mitchell BD, Leicher SB, Wagner AL, O'Brian JT, Georges LP. Epidemiology of the complications of diabetes. In: Leslie RDG, Robbins DC, editors. *Diabetes: Clinical Science in Practice*. Cambridge: Cambridge University Press, 1995:221–287.
3. Ziegler D, Fies FA, Spuler M, Lessmann F. The epidemiology of diabetic neuropathy: Diabetic Cardiovascular Autonomic Neuropathy Multicenter Study Group. *J Diabetes Complications* 1992; 6:49–57.
4. Pfeifer MA, Weinberg CR, Cook DL, et al. Autonomic neural dysfunction in recently diagnosed diabetic subjects. *Diabetes Care* 1984; 7:447–445.
5. Ewing DJ, Boland O, Neilson JM, Cho CG, Clarke BF. Autonomic neuropathy, QT interval lengthening, and unexpected deaths in male diabetic patients. *Diabetologia* 1991; 34:182–185.
6. Rathmann W, Ziegler D, Jahnke M, Haastert B, Gries FA. Mortality in diabetic patients with cardiovascular autonomic neuropathy. *Diabet Med* 1993; 10:820–824.
7. O'Brian IA, McFadden JP, Corral RJ. The influence of autonomic neuropathy on mortality in insulin-dependent diabetes. *Q J Med* 1991; 79:495–502.
8. Sundkvist G, Lilja B. Autonomic neuropathy predicts deterioration in glomerular filtration rate in patients with IDDM. *Diabetes Care* 1993; 16:773–779.
9. Wirta OR, Pasternack AI, Mustonen JT, Laippala PJ, Reinikainen PM. Urinary albumin excretion rate is independently related to autonomic neuropathy in type 2 diabetes mellitus. *J Intern Med* 1999; 245:329–335.
10. Toyro JP, Niskanen LK, Lansimies EA, et al. Autonomic neuropathy predicts the development of stroke in patients with non-insulin-dependent diabetes mellitus. *Stroke* 1996; 27:1316–1318.
11. Schumer MP, Joyner SA, Pfeifer MA. Cardiovascular autonomic neuropathy testing in patients with diabetes. *Diabetes Spectrum* 1988; 11:227–223.
12. Purewal TS, Watkins PJ. Postural hypotension in diabetic neuropathy: a review. *Diabet Med* 1995; 12:192–200.
13. Roy TM, Peterson HR, Snider HL, et al. Autonomic influence on cardiovascular performance in diabetic subjects. *Am J Med* 1989; 87:382–388.
14. Burgos LG, Ebert TJ, Asiddao C, et al. Increased intraoperative cardiovascular morbidity in diabetics with autonomic neuropathy. *Anesthesiology* 1989; 70:591–597.
15. Langer A, Freeman MR, Josse RG, Steiner G, Armstrong PW. Detection of silent myocardial ischemia in diabetes mellitus. *Am J Cardiol* 1991; 67:1073–1078.
16. Ziegler D, Gries FA, Muhlen H, Rathmann W, Spuler M, Lessmann F. Prevalence and clinical correlates of cardiovascular autonomic and peripheral diabetic neuropathy in patients attending diabetes center. The DiaCAN Multicenter Study Group. *Diabet Metab* 1993; 19:143–151.
17. Ziegler D. Cardiovascular autonomic neuropathy. Clinical manifestations and measurement. *Diabetes Rev* 1999; 7:342–357.



18. May O, Arildsen H, Damsgaard EM, Mickley H. Cardiovascular autonomic neuropathy in insulin-dependent diabetes mellitus: prevalence and estimated risk of coronary heart disease in the general population. *J Intern Med* 2000; 248:483–491.
19. Diabetes Control and Complications Trial Research Group. The effect of intensive diabetes therapy on measures of autonomic nervous system function in the Diabetes Control and Complications Trial (DCCT). *Diabetologia* 1998; 41:416–423.
20. Ewing DJ, Campbell IW, Clarke BF. The natural history of diabetic autonomic neuropathy. *Q J Med* 1980; 49:95–108.
21. Veglio M, Borra M, Stevens LK, Fuller JH, Perin PC. The relation between QTc interval prolongation and diabetic complications. The EURODIAB IDDM Complications Study Group. *Diabetologia* 1999; 42:68–75.
22. Nakano S, Uchida K, Kigoshi T, et al. Circadian rhythm of blood pressure in normotensive NIDDM subjects: its relationship to microvascular complications. *Diabetes Care* 1991; 14:707–711.
23. Airaksinen KEJ, Koistinen MJ. Association between silent coronary artery disease, diabetes, and autonomic neuropathy: fact or fallacy? *Diabetes Care* 1992; 15:288–292.
24. Marchant B, Umachandran V, Stevenson R, Kopelman PG, Timmis AD. Silent myocardial ischemia: role of subclinical neuropathy in patients with and without diabetes. *J Am Coll Cardiol* 1993; 22:1433–1437.
25. Faerman I, Faccio E, Milei J, et al. Autonomic neuropathy and painless myocardial infarction in diabetic patients. Histologic evidence of their relationship. *Diabetes* 1977; 26:1147–1158.
26. Solar NG, Bennett MA, Pentecost BL, Fitzgerald MG, Malins JM. Myocardial infarction in diabetes. *Q J Med* 1975; 173:125–131.
27. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Morning peak in the incidence of myocardial infarction: experience in the ISIS-2 trial. *Eur Heart J* 1992; 13:594–598.
28. Aronson D, Weinrauch LA, D'Elia JA, et al. Circadian patterns of heart rate variability, fibrinolytic activity, and hemostatic factors in type I diabetes mellitus with cardiac autonomic neuropathy. *Am J Cardiol* 1999; 84:449–453.
29. Ewing DJ, Neilson JM, Shapiro CM, Stewart JA, Reid W. Twenty four hour heart rate variability: effects of posture, sleep, and time of day in healthy controls and comparison with bedside tests of autonomic function in diabetic patients. *Br Heart J* 1991; 65:239–244.
30. Ziegler D. Cardiovascular autonomic neuropathy: clinical manifestations and measurement. *Diabet Rev* 1999; 7:342–357.
31. The Diabetes Control and Complications Trial Research Group. The effect of intensive diabetes therapy on measures of autonomic nervous system function in the Diabetes Control and Complications Trial (DCCT). *Diabetologia* 1998; 41:416–423.
32. Burger AJ, Weinrauch LA, D'Elia JA, Aronson D. Effect of glycemic control on heart rate variability in type I diabetic patients with cardiac autonomic neuropathy. *Am J Cardiol* 1999; 84:687–691.
33. Gaede P, Vedel P, Parving HH, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. *Lancet* 1999; 353:617–622.
34. Hansen KW. Diurnal blood pressure profile, autonomic neuropathy and nephropathy in diabetes. *Eur J Endocrinol* 1997; 136:35–36.
35. Ziegler D, Schatz H, Conrad F, Gries FA, Ulrich H, Reichel G. Effects of treatment with the antioxidant alpha-lipoic acid on cardiac autonomic neuropathy in NIDDM patients. A 4-month randomized controlled multicenter trial (DEKAN Study). *Diabetes Care* 1997; 20:369–373.
36. Ikeda T, Iwata K, Tanaka Y. Long-term effect of epalrestat on cardiac autonomic neuropathy in subjects with non-insulin dependent diabetes mellitus. *Diabetes Res Clin Pract* 1999; 43:193–198.
37. Vinik AI, Glass LC. Diabetic autonomic neuropathy. In: Davidson JK, editor. *Clinical Diabetes Mellitus: A Problem-Oriented Approach*. 3rd ed. New York: Thieme, 1999: 637–647.
38. Makimätilä S, Mantysaari M, Schlenzka A, Summanen P, Yki-Jarvinen H. Mechanism of altered hemodynamic and metabolic responses to insulin in patients with insulin-dependent diabetes mellitus and autonomic dysfunction. *J Clin Endocrinol Metab* 1998; 83:468–475.
39. Stansberry KB, Shapiro SA, Hill MA, McNitt PM, Meyer MD, Vinik AI. Impaired peripheral vasomotion in diabetes. *Diabetes Care* 1996; 19:715–721.
40. Stansberry KB, Shapiro SA, Hill MA, McPitt PM, Meyer MD, Vinik AI. Impairment of peripheral blood flow responses in diabetes resembles an enhanced aging effect. *Diabetes Care* 1997; 20:1711–1716.
41. Stansberry KB, Peppard HR, Babyak LM, Popp G, McNitt PM, Vinik AI. Primary nociceptive afferents mediate the blood flow dysfunction in non-glabrous (hairy) skin of type 2 diabetes. A new model for the pathogenesis of microvascular dysfunction. *Diabetes Care* 1999; 22:1549–1554.
42. Abrahamsson H. Gastrointestinal motility disorders in patients with diabetes mellitus. *J Intern Med* 1995; 237:403–409.
43. Koch KL. Diabetic gastropathy: gastric neuromuscular dysfunction in diabetes mellitus: a review of symptoms, pathophysiology, and treatment. *Dig Dis Sci* 1999; 44:1061–1075.
44. Spangeus A, El-Salhy M, Suhr O, Eriksson J, Lithner F. Prevalence of gastrointestinal symptoms in young and middle-aged diabetic patients. *Scand J Gastroenterol* 1999; 34:1196–1202.
45. Maleki D, Camilleri M, Burton DD, et al. Pilot study of pathophysiology of constipation among community diabetics. *Dig Dis Sci* 1998; 43:2373–2378.
46. Horowitz M, Edelbroek M, Fraser R, Maddox A, Wishart J. Disordered gastric motor function in diabetes mellitus. Recent insights into prevalence, pathophysiology, clinical relevance, and treatment. *Scand J Gastroenterol* 1991; 26:673–684.
47. Gentry P, Miller P. Nutritional considerations in a patient with gastroparesis. *Diabetes Educ* 1989; 15:374–376.
48. Vinik A, Erbas T, Stansberry K. Gastrointestinal, genito-urinary, and neurovascular disturbances in diabetes. *Diabetes Rev* 1999; 7:358–378.
49. Erbas T, Varoglu E, Erbas B, Tastekin G, Akalin S. Comparison of metoclopramide and erythromycin in the treatment of diabetic gastroparesis. *Diabetes Care* 1993; 16:1511–1514.
50. Valdovinos MA, Camilleri M, Zimmerman BR. Chronic diarrhea in diabetes mellitus: mechanisms and an approach to diagnosis and treatment. *Mayo Clin Proc* 1993; 68:691–702.
51. Verne GN, Sninsky CA. Diabetes and the gastrointestinal tract. *Gastroenterol Clin North Am* 1998; 27:861–874.
52. McCulloch DK, Campbell IW, Wu FC, Prescott RJ, Clarke BF. The prevalence of diabetic impotence. *Diabetologia* 1980; 18:279–283.
53. Rendell MS, Rajfer J, Wicker PA, Smith MD. Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial. Sildenafil Diabetes Study Group. *JAMA* 1999; 281:421–426.
54. Enzlin P, Mathieu C, Vanderschueren D, Demyttenaere K. Diabetes mellitus and female sexuality: a review of 25 years' research. *Diabet Med* 1998; 15:809–815.
55. Joshi N, Caputo GM, Weitekamp MR, Karchmer AW. Infections in patients with diabetes mellitus. *N Engl J Med* 1999; 341:1906–1912.
56. Shaw JE, Abbott CA, Tindle K, Hollis S, Boulton AJ. A randomized controlled trial of topical glycopyrrolate, the first specific treatment for diabetic gustatory sweating. *Diabetologia* 1997; 40:299–301.
57. Meyer C, Grossmann R, Mitrouk A, et al. Effects of autonomic neuropathy on counterregulation and awareness of hypoglycemia in type 1 diabetic patients. *Diabetes Care* 1998; 21:1960–1966.
58. Vinik AI. Diagnosis and management of diabetic neuropathy. *Clin Geriatr Med* 1999; 15:293–320.

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