Diabetic Neuropathy

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This is the seventh in a series of articles based on presentations at the American Diabetes Association's 67th Scientific Sessions, 22–26 June 2007, Chicago, Illinois, that discuss aspects of diabetic foot wounds and neuropathy.

Hyperbaric oxygen

In a debate on whether hyperbaric oxygen is beneficial in the healing of diabetic foot wounds, Anthony Berendt (Nutfield, U.K.) suggested it not to be appropriate, while Harriet Hopf (Salt Lake City, UT) argued that it is an evidence-based appropriate approach for treating certain people with severe diabetic food wounds. As discussed in last month's column, the diabetic foot is an important problem. In a series of 449 patients with diabetic foot wounds, 352 were superficial and 134 of these were neither ischemic nor infected. A total of 183 ulcers were clinically infected, and 216 patients had arterial insufficiency. At 6 and 12 months, 247 and 295 of the ulcers had healed without amputation, with median time to healing 78 days; 6 and 8% required amputation and an additional 6 and 11% of the patients had died at the two time points, suggesting high morbidity and mortality associated with diabetic foot wounds (1). Using a Medicare database, the average expenditure for a diabetic person with a lower-extremity ulcer in 1995–1996 was over $15,000, approximatley three times that for a diabetic person without ulceration (2).

Berendt referred to the use of hyperbaric oxygen as "myth," in the sense of being a widely held but false notion, suggesting that although the approach is used in perhaps 800 facilities in the U.S., data showing efficacy is lacking. "There is poor evidence of effectiveness or of cost-effectiveness," he stated, pointing out that the use of this approach dates to the 1600s with use of pressurized chambers for treatment of individuals with respiratory disease, with approaches to use of oxygen at high pressure beginning more than 200 years ago, leading to recognition of some of the hazards of exposure to pressurized air. Use of this approach for decompression sickness and for gas gangrene has been valuable, and the use of hyperbaric oxygen has been thought beneficial for other conditions by increasing oxygen delivery from plasma. Other mechanisms of benefit may include local vasoconstriction and increase in local growth factor levels. There is evidence of benefit in diabetic foot wounds complicated either by osteomyelitis or by soft tissue infection. Berendt alluded, however, to a long association of the treatment with what he suggested might be somewhat disreputable medical care, with what he termed a lack of convincing evidence of benefit in diabetic foot wounds without evidence of infection, although such lesions have been recommended as targets for the treatment. He pointed out that uncontrolled clinical reports are unlikely to lead to unbiased data, as patients who are treated with this very expensive approach are likely to have better health care access and to be more compliant. The best source of information, Berendt stated, is a Cochrane review that included only five randomized controlled trials, four of which were relevant to the diabetic foot. The two largest studies scored poorly in terms of methodology. Of the other two studies, one did not address clinical end points, and the smaller clinical trial showed no evidence that amputations were avoided (3).

Berendt concluded that although there is a body of evidence that ulcers heal more rapidly and that there is a reduced amputation rate with hyperbaric oxygen, there appears to be bias in the available trials. Furthermore, he implied that that there are some 20 million people with diabetes in the U.S., so that if one million individuals have foot ulcers, and one-third potentially would benefit from hyperbaric oxygen, at a cost of each treatment course of approximately $20,000; $7 billion would be spent on this treatment annually. Indeed, he noted that hospitals and even outpatient facilities appear to be opening hyperbaric treatment units because of the high potential for profit. With this very high potential cost, he concluded, hyperbaric therapy has not been adequately documented to be a reasonable approach to treatment.

Hopf argued in favor of hyperbaric oxygen treatment, stating that this therapy specifically addresses the mechanisms that appear involved in diabetic foot wounds and that, in her opinion, there is clinical trial evidence that severe ulcers with risk of amputation can be treated with this approach with benefit. Diabetic foot ulcers account for ~65% of amputations, with poor healing related to vasomotor dysfunction and abnormal transfer of oxygen into tissues. Neuropathy may lead to repetitive trauma, but there is also impaired resistance to infection, abnormal tissue perfusion, and abnormalities of inflammation with fibroblasts from diabetic patients showing delayed proliferation. Certainly, she agreed, medical evaluation for neuropathy, ischemia, and infection are crucial, with glycemic control and debridement, offloading, proper moist wound care, and smoking cessation all basic, but, even with such optimal approaches, one-third of chronic foot wounds in diabetic patients fail to heal, and amputations cannot be prevented. In this context, adjunctive therapies play important roles.

Hyperbaric oxygen is usually administered at least at twice atmospheric pressure, with at least 30 treatments required to promote angiogenesis. Barotrauma with ear injury occurs in 2–4% of patients, and pulmonary barotrauma causing pneumothorax or gas embolism is extremely rare. Seizure occurs at approximately seven times atmospheric pressure, but are not felt to be caused by the lower levels used in treatment. Other infrequent adverse effects include hypogly-

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Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; 5-HT, 5-hydroxytryptamine.

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cemia, a form of transient myopia, and worsening of uncontrolled congestive heart failure, which is a contraindication to the approach. In addition, some people experience extreme claustrophobia and cannot tolerate the units. Decompression sickness due to formation of intravascular nitrogen bubbles does not occur, as only pure oxygen is administered. Hopf described as crucial the use of transcutaneous oximetry. The normal transcutaneous oxygen level is 50–70 mm mercury, with a level <20 associated with more than a 100-fold increase in risk of amputation.

When such wounds are treated with hyperbaric oxygen, transiently, tissue oxygen levels around 500 mmHg may be seen. If levels do not increase at least to 100 mmHg, it is unlikely that healing will occur. Hopf noted, though, that simple delivery of oxygen to ischemic tissue is unlikely to be the direct mechanism of benefit, as it only takes place for several hours per day. Rather, she suggested, hyperbaric oxygen should be considered in essence a pharmacologic approach, which increases neutrophil bacteriocidal activity, increases angiogenesis, increases growth factor levels, and decreases leukocyte adhesion, so potentially promoting an appropriate inflammatory response in the diabetic foot wound. She reviewed, in somewhat more detail than did Berendt, the relevant intervention studies, with transcutaneous oxygen measurements at the beginning of the trials ~20 in both groups, increasing threefold among those receiving hyperbaric oxygen, implying that the approach increases local perfusion, perhaps by stimulating angiogenesis. She suggested that for individuals whose baseline transcutaneous oxygen level is >40, it is unlikely that hyperbaric oxygen will be helpful. In the Cochrane meta-analysis of 118 patients treated for severe diabetic foot wounds (3), there was excellent likelihood of response to hyperbaric oxygen as an adjunctive treatment for diabetic foot ulcers of Wagner (4) grade III (deep wounds with osteomyelitis) or higher (wounds with partial or complete foot gangrene).

In those patients, for whom this form of treatment is appropriate, Hopf suggested hyperbaric oxygen is cost-effective and, if more widely utilized, would improve outcome at reduced overall cost. She stressed the need for use of appropriate selection guidelines as to wound severity and transcutaneous oxygen concentration. There is an accreditation mechanism by which the Hyperbaric Medicine Society certifies that a center is able to deliver the treatment, although Hopf acknowledged that participation is currently voluntary, and that many of the facilities performing this treatment currently do not adhere to the guidelines she described. "The data are there," she said, emphasizing that while "it's not the final answer, there is enough to say that this is a treatment. . . that demonstrates a benefit." It should be noted that the *Medicare National Coverage Determinations Manual* relevant criteria for coverage are for "chronic refractory osteomyelitis, unresponsive to conventional medical and surgical management," and for "diabetic wounds of the lower extremities in patients who . . . [have] a wound classified as Wagner grade III or higher; and . . . failed an adequate course of standard wound therapy. . . after there are no measurable signs of healing for at least 30 days of treatment" (5). It would appear that Hopf's recommendations are congruent with these guidelines, and that if the treatment is, as Berendt implied, inappropriately used at some facilities to treat patients with less severe wounds, there already exists a mechanism for withholding of reimbursement.

Types of diabetic neuropathy

Douglas Zochodne (Calgary, Canada) reviewed the differential diagnosis of diabetic neuropathy, noting that approximately half of diabetic patients have evidence of neuropathy, so that the prevalence of diabetic neuropathy is some 100-fold greater than the combined prevalence of degenerative neurologic conditions such amyotrophic lateral sclerosis and Parkinson's disease. Diabetic motor and sensory polyneuropathy may be classified into a number of types, including distal symmetrical neuropathy, particularly with sensory abnormalities mainly involving small nerve fibers; mixed motor and sensory neuropathy, the most common type, comprising ~70% of cases of neuropathy, although nearly half appear to be particularly predominantly sensory and involve large nerve fibers; mixed motor-sensory-autonomic neuropathy; predominantly autonomic neuropathy; the rare predominantly motor neuropathy; and focal and multifocal asymmetric neuropathies of a variety of types. The sensory phenotype is largely length-dependent, so that symptoms of paresthesia, pain, and sensory loss occur most often in the distal lower extremities. This form of neuropathy was well described by R Wayne Rundles in the 1940s, as occurring early in the course of diabetes, often within months of onset, and affecting diabetic children with what is likely a higher frequency than clinically recognized (6).

Autonomic neuropathy also exhibits length dependence, leading to the easily damaged dry feet characteristic of the diabetic patient. The differential diagnosis of sensory polyneuropathy includes many conditions, such as hypothyroidism, vitamin B12 and thiamine deficiency, and other nutritional neuropathies, particularly alcohol-related and post gastrectomy. Neuropathy may be associated with sarcoidosis, with anti–myelin-associated glycoproteins, or with monoclonal gammopathies; may represent a paraneoplastic syndrome; and may be seen in early chronic inflammatory demyelinating polyneuropathy (CIDP). Spinal stenosis, with or without carpal tunnel syndrome, may present as a pseudo-neuropathy. Toxins, human immunodeficiency virus, early forms of vasculitis and connective tissue diseases, amyloid, and inherited neuropathies such as Charcot-Marie-Tooth are additional possibilities. Potential screening tests might include a complete blood count, sedimentation rate, vitamin B12, thyroid stimulating hormone, protein electrophoresis, homocysteine, and methylmalonic acid level, as well as electrophysiologic testing, although a cookbook approach to screening is much less useful than a high level of diagnostic suspicion for people with significant or progressive disease. One must ask, "Does it fit?" Does the sensory component exceed the degree of motor loss, are there other neurologic abnormalities, is control of glycemia good, is the syndrome subacute, and is there weight loss or other evidence of another systemic illness?

CIDP typically affects motor nerves to a greater extent than sensory, and may be progressive or relapsing, with evidence of prominent demyelination seen on electrophysiological tests, although it is important to note that multiple sites must be tested. There is an elevation in cerebrospinal fluid protein level and demyelination on nerve biopsy, with the disease responsive to steroids, to intravenous immunoglobulin, and to plasma exchange. There may be an increased prevalence of the syndrome in diabetes, and certainly diabetes does not prevent the condition, leading Zochodne to note that it is important to consider this entity in appropriate

diabetic patients. He stressed the importance of neurologic assessment of all diabetic patients, with monofilament testing useful, as is the use of quantitative sensory testing of vibration sensation, although this is not routinely available. Epidermal skin biopsy is a new technique being studied which may be useful (7), as is confocal microscopy of nerve fibers in the cornea (8). Zochodne pointed out that neuropathy may be associated with impaired glucose tolerance, and that this syndrome may be associated with neuropathic pain, although Zochodne did point out that "further work is needed." Certainly, there are age-related effects on the peripheral nervous system, and although he did not believe that one could diagnose "a neuropathy just because of age," Zochodne agreed that age with diabetes certainly can increase the likelihood of neuropathy.

Compression nerve injuries are also more common in individuals with diabetes and can be debilitating. These include carpal tunnel syndrome, ulnar neuropathy due to entrapment at the elbow (with consequent loss of intrinsic muscle function in the hand), and peroneal neuropathy with foot drop. Intercostals neuropathies can mimic abdominal visceral emergencies, and lumbosacral plexopathy may be associated with prolonged pain, with all of these syndromes requiring a variety of medical and, on occasion, surgical therapies.

Several studies presented at the ADA meeting addressed aspects of diabetic neuropathy. Jurado et al. (abstract 784) measured plasma levels of the NH_2-terminal fragment of the brain natriuretic peptide in 100 type 2 diabetic people, showing significant correlation with age and with the presence of cardiovascular disease. By correcting for these factors, however, levels correlated with the presence of diabetic peripheral neuropathy. (Abstract numbers refer to the American Diabetes Association Scientific Sessions, *Diabetes* 56 [Suppl. 1], 2007.) Atkin et al. (abstract 800) analyzed data from the Diabetes Control and Complications Trial (DCCT), in which 149 of 1,245 patients assessed at 5 years developed neuropathy. There was a 4% increase in neuropathy per centimeter increase in height among conventionally treated patients, while the relationship of neuropathy to height was not significant in the intensive treatment group. Height was not significantly related to either retinopathy or nephropathy. Pradeepa et al. (abstract 303) reported aspects of diabetic neuropathy in the Indian Chennai Urban Rural Epidemiology Study. This study included 1,382 previously known and 354 newly detected diabetic patients. Using vibratory perception threshold measurement, 11% had neuropathy, affecting 12% of known versus 7% of newly diagnosed patients. Retinopathy and proteinuria were associated with a doubling of likelihood of neuropathy.

Davis et al. (abstract 4) followed 531 type 2 diabetic individuals for 5–8 years, finding that use of either a statin or a fibrate were associated with a 48 and 35% respective reduction in the likelihood of peripheral sensory neuropathy, independent of their effects on lipid levels. Ziegler et al. (abstract 7) treated 460 diabetic people with mild-to-moderate distal symmetric polyneuropathy with α-lipoic acid 600 mg daily or placebo for 4 years, finding significant improvement versus worsening in clinical measures of peripheral motor and sensory neuropathy, although the degree of worsening among control patients was modest. There was no improvement in nerve conduction.

Diabetic sympathetic neuropathy

Martin Stevens (Birmingham, U.K.) discussed sympathetic dysfunction in diabetes, suggesting its relationship to a number of diabetic complications. Neuropathy is present in up to 70% of individuals with diabetes, and may be seen in the prediabetic stage (9). Autonomic dysfunction, however, has not been as well studied as peripheral neuropathy. Diabetes results in a form of small-fiber neuropathy, affecting autonomic nerve fibers. The cardiovascular system and lower limb both may be affected by abnormalities of the sympathetic nervous system. Cardiac metabolism utilizes glucose, amino acids, ketones, and fatty acids, with increased fatty acid levels in diabetes, potentially requiring greater levels of oxygen consumption and potentially contributing to cardiac energy depletion. Stevens presented case studies illustrating the roles of sympathetic dysfunction as a presenting feature of diabetes, and in relationship to early cardiovascular dysfunction in diabetes, potentially predisposing to heart failure.

First, he discussed a 46-year-old male with hyperhydrosis. He was referred to his endocrine clinic with mild hypertension and with sympathetic hyperreactivity on autonomic function testing, and showed lack of the expected nocturnal fall in blood pressure. He was found to have diabetes on glucose tolerance testing, and he responded to treatment with clonidine.

Cardiomyopathy, Stevens said, is a contributing factor to heart failure in people with diabetes, with heart failure three to five times more frequently seen in individuals with than without diabetes. Autonomic dysfunction may well contribute to this, with hypertension as a risk factor for heart failure, which is typically unrecognized when only occurring during the night. Other potential causes of heart failure in individuals with diabetes include microvascular disease and oxidative stress, as well as the increased prevalence of coronary artery disease. Dysfunction of the sympathetic nervous system may also contribute to heart failure in diabetes. ^{11}C-meta-hydroxyephedrine positron emission tomographic imaging may be used to visualize sympathetic neurons (10). This radiolabeled analog of norepinephrine competes for reuptake into nerve terminals, giving a marker of sympathetic tone and of sympathetic nerve fiber density. In a comment about ^{123}I-metaiodobenzylguanidine single-photon emission computed tomography scanning, Stevens noted that this is also a reasonable tool for cardiac sympathetic imaging, but that it is more difficult with this imaging agent to correct for inhomogeneity of myocardial perfusion.

In type 1 diabetes there is evidence of increased left ventricular sympathetic tone with such imaging, despite normal results of conventional tests of autonomic function, with this abnormality associated with diastolic dysfunction (11). Increased sympathetic tone may lead to small-vessel damage and is associated with decreased myocardial perfusion reserve. In people with type 2 diabetes, within the first 1–2 years after diagnosis, more than half of the left ventricle shows increased sympathetic tone with such studies. This may be a reflex response to central activation of the sympathetic nervous system, and may lead to increased oxidative stress and to loss of cardiomyocytes.

In the lower limb, edema, pain, and erythema may be caused by increased sympathetic tone, with decreased sweating, leading to dry and cracked skin, with lower-limb osteoporosis and increased risk of fracture, and with a relationship to development of Charcot arthropathy. Bone density is reduced by 15–20% in individuals with type 1 diabetes, with in-

NEWS FROM THE FOOD AND DRUG ADMINISTRATION

From time to time, new announcements by the FDA pertaining to aspects of diabetes treatment will be highlighted in this section.

On 18 January 2008, the FDA approved a modification to the prescribing information for the bile acid binding resin colesevelam, agreeing that its glucose-lowering properties are sufficient to warrant adding this effect as an additional indication for its use. When administered in a dose of six 625-mg tablets daily, the new information states that in combination with metformin, the placebo-adjusted decrease in A1C was 0.5%, from a baseline of 8.1%. In combination with sulfonylurea, the placebo-adjusted A1C decreased by 0.8% from a baseline of 8.2%, and in combination with insulin the placebo-adjusted A1C decreased by 0.6% from a baseline of 8.2%. The FDA approval letter is available at http://www.fda.gov/cder/foi/appletter/2008/021176s017ltr.pdf and the revised prescribing information at http://www.fda.gov/cder/foi/label/2008/021176s0171bl.pdf (both accessed 27 January 2008).

creased sympathetic tone contributing to elevated rates of bone turnover.

Later cardiovascular effects of sympathetic dysfunction include an elevation in resting heart rate, which may be associated with either decreased parasympathetic or increased sympathetic tone. Impaired exercise tolerance may be seen in this setting, and there is an association of sudden death with sympathetic dysfunction, although the assumption of causality is difficult to demonstrate given the many associated diabetic complications in such patients. Stevens presented a second case, a 26 year-old woman who had had type 1 diabetes for 12 years, with background retinopathy, albuminuria, tachycardia, and anemia. ^{11}C-metahydroxyephedrine positron emission tomography was abnormal, with globally decreased left ventricular sympathetic innervation, but with one area showing increased sympathetic innervation, potentially causing left ventricular instability and increasing risk of arrhythmia.

Multifactorial intervention in the Steno study with pharmacologic therapy that targeted hyperglycemia, hypertension, dyslipidemia, and microalbuminuria, along with aspirin, reduced the risk of autonomic neuropathy by 63% (12). Treatment of cardiovascular autonomic neuropathy in people with diabetes with orthostatic hypotension includes midodrine, erythropoietin, fludrocortisone, octreotide, and simply elevating the head of the bed during the night to prevent supine hypertension. Agents to reduce cardiac fatty acid utilization are being studied. Stevens noted that treatment of denervation tachycardia is quite difficult.

Two studies reported at the ADA meeting addressed relevant aspects of diabetic neuropathy. Lomax and Jones (abstract 261) prospectively studied the incidence of Charcot arthropathy, defined by a swollen, warm, neuropathic foot with bounding pulses, in a U.K. population followed from 1996 to 2006, finding an annual incidence of three cases per 10,000 diabetic individuals. After treatment with casting for 5–8 months, three-quarters of patients were weaned to footwear while ~10% required surgical removal of bone and an additional 10% died or had an amputation. Jirkovská et al. (abstract 260) found evidence of vitamin D deficiency in association with increased bone reabsorption in 38 diabetic people with acute Charcot arthropathy.

Gene therapy for neuropathy and neuropathic pain

David Fink (Ann Arbor, MI) discussed preclinical studies of gene therapy for neuropathy and neuropathic pain. Diabetic polyneuropathy involves "dying back" of sensory motor fibers, with to date no effective treatment, although control of hyperglycemia does slow the rate of deterioration. Peptide neurotrophic factors can be used, although nerve growth factor studies in animal models involved several orders of magnitude higher doses than have been possible in humans. Such levels of treatment could be attained by direct delivery of trophic factors to involved nerves, perhaps with gene therapy by injecting a vector from which the desired genes would be taken up directly. Potential vectors include liposomes, and retrovirus and adenovirus. Fink noted that herpes simplex virus might be an idea vector for such treatment, as it is naturally taken up in sensory neuronal nuclei, remaining in this location through the lifetime of the host, and carried by retroaxonal transport form nerve fibers to the nucleus. Deletion of one of the early viral protein genes abolishes replication and infectivity, further suggesting this to be a potentially useful approach. In a pyridoxine overdose animal model, a vector expressing neurotrophin 3 was administered before pyridoxine, finding that this approach prevented weakness and histological abnormality in the model, which can be considered "proof of principle." With a latency promoter to allow long-term gene expression, the vector was administered 5 months before pyridoxine, again preventing the toxic neuropathy. In a streptozotocin-diabetic mouse model, with vector administered 2 weeks after onset of diabetes, over 6 months electrophysiology showed preservation of nerve function despite hyperglycemia. Dermal innervation, which is largely lost in diabetic animals, was preserved with treatment. A human trial is planned in painful neuropathy.

In a study presented at the ADA meeting, Wessels et al. (abstract 3) found cognitive performance of type 1 diabetic patients was reduced in proportion to reduction in the ratio of white matter to total intracranial volume on MRI scanning, with the anatomic lesion more pronounced in those with retinopathy, suggesting a relationship between microvascular disease and loss of brain function. Gandhi et al. (abstract 2) studied brain proton magnetic resonance spectroscopy in 71 type 1 diabetic men, finding that those with painful peripheral neuropathy had similar levels of thalamic neuronal function to those without neuropathy, while painless neuropathy was associated with reduced thalamic function, suggesting that relative preservation of thalamic neuronal function is required for the transmission of abnormal peripheral signals that leads to pain perception. Obrosova et al. (abstract 1) found evidence of hyperalgesia, allodynia, and intraepidermal nerve fiber degeneration in diabetic mice, with these abnormalities attenuated in diabetic mice either not expressing or treated with an inhibitor (GPI-15427; MGI Pharma, Baltimore, MD) of a poly(ADP-ribose) polymerase enzyme, which functions by binding to DNA breaks. Presumably, overactivation of the enzyme in response to oxidant- and free radical–mediated excessive DNA single-

strand breaks in diabetes promotes neuronal dysfunction and cellular damage.

Wymer et al. (abstract 596) administered the anticonvulsant lacosamide to 370 individuals with painful distal diabetic neuropathy, finding improvement in subjective pain assessment, though with dose-related adverse symptoms of dizziness, nausea, fatigue, headache, and tremor. Schwartz (abstract 608) treated 147 people having painful diabetic neuropathy with extended-release gabapentin (3 g daily) or placebo, finding reduction in pain score and improvement in sleep when administered once daily, although 17 and 12% of individuals who received the once-daily dosing experienced dizziness and somnolence, respectively.

Diabetic gastroparesis

Brian Lacy (Dartmouth, NH) discussed diabetic gastroparesis, addressing its epidemiology, etiology, and pathophysiology; a cost-effective evaluation approach; and current treatment options. He drew a distinction between gastroparesis and gastropathy, the former defined by delayed gastric emptying in the absence of obstruction. Normal gastric emptying requires coordination of extrinsic neurons, enteric motor neurons, smooth muscle cells, and interstitial cells of Cajal. Multiple abnormalities contribute to the pathogenesis of gastroparesis. Symptoms may be caused by dysfunction of the vagus nerve; by loss of interstitial cells of Cajal; by injury to the enteric nervous system pacemaker; perhaps by microangiopathy (though this is controversial); and by smooth muscle injury, perhaps caused by insulin deficiency or by abnormal humoral factors such as nitric oxide, calcitonin gene-related peptide, substance P, and neuropeptides Y. It is important to note that hyperglycemia contributes to symptoms by slowing gastric emptying, even without autonomic neuropathy, inhibiting antral pressure waves in both the fed and fasted states. Thus, abnormal gastric emptying motor function produces abnormal relaxation of the proximal stomach, with increases in amplitude of pyloric pressure waves and induction of gastric dysrhythmia.

Gastroparesis, Lacy said, affects ~10 million people in the U.S., with half the cases idiopathic (of which 80% occur in women) and the other half occurring in individuals with diabetes. Symptoms are seen in 20–55% of people with diabetic gastroparesis, to a lesser extent in those with type 2 than with type 1 diabetes, in association with microvascular complications. These symptoms are associated with significant deterioration in quality of life. Lacy reviewed a survey of 398 diabetic individuals, excluding those with known depression. Gastroparesis was associated with depressive symptoms. People with gastroparesis had increased risk of bezoar and of gastroesophageal reflux, occasionally developing a Mallory Weiss tear. The likelihood of cholecystectomy was markedly increased. Gastroparesis is associated with considerable economic burden. In a survey of 491 patients, 28% had decreased income, 11% were disabled because of gastroparesis, and 19% required placement of a feeding jejeunostomy tube.

Symptoms include nausea in 92%, epigastric pain in 85%, vomiting in 84%, bloating in 75%, early satiety in 60%, anorexia and weight loss in >50%, and reflux symptoms in >50%, although none of these symptoms are specific. The diagnosis is established by history, examination (a succussion splash should be considered normal, however, acutely after ingesting a large volume of fluid), a flat-plate X-ray of the abdomen for individuals with obstructive symptoms, and esophagogastroduodenoscopy and a solid-phase gastric emptying study if symptoms persist. Ultrasound may be used to measure gastric emptying, but an upper gastrointestinal series is not useful either in assessment of gastric emptying or in detecting complications such as ulceration.

A gastric emptying study must be carried out for at least 2 h, and ideally for 4 h, with results reported as the percentage of a standard meal retained at 1, 2, 3, and 4 h. There is large interindividual variation, and results are influenced by the blood glucose at the time of study, by obesity, by sex, and by the stage of the menstrual cycle in women. Furthermore, there is poor correlation between symptoms and the gastric emptying time. The erythromycin derivative ABT-229, which acts on motilin receptors, increases gastric emptying but fails to improve symptoms. Lacy reviewed a study of 20 people with gastroparesis, following symptoms and autonomic nerve testing over 12 years, showing that autonomic function deteriorated over time.

A number of treatment approaches have been developed. It is important to check for a bezoar. These are difficult to lyse during endoscopy, but if surgery is required there may be as great as a 10% mortality, so the use of a low-fiber diet is particularly important for these patients. The diet should consist of small, frequent meals, low in fat and fiber, with emphasis on ingestion of liquids, particularly when there is a flare in symptoms.

A large variety of pharmacologic approaches have been used for gastroparesis, none with great success. The use of prokinetic treatment is controversial. Metoclopramide increases acetylcholine release, but 30–40% of treated individuals experience side effects, including anxiety, depression, and change in cognitive function. Erythromycin does increase motility, but does not change symptoms. Domperidone is not available in the U.S., but appears to be relatively effective, and lacks central nervous system side effects. Tegaserod is a 5-hydroxytryptamine (5-HT)-4 receptor agonist for irritable bowel syndrome in women and has been used in people with gastroparesis, although it may have potential cardiovascular side effects (13,14). Cisapride is a mixed 5-HT3 antagonist and 5-HT4 agonist. It is not available now because of concern about cardiac arrhythmias. Antiemetic therapies used in gastroparesis include the phenothiazine derivative prochlorperazine, the antihistamine meclizine, the anticholinergic scopolamine, metoclopramide, and the 5-HT3 receptor antagonist ondansetron. Sildenafil has effect in animal models, but at this point has not been shown to be effective in clinical treatment. There is no good evidence of benefit from use of somatostatin analogs. There is a role for use of narcotic analgesics, Lacy said, pointing out that "these patients hurt, they are in pain," but narcotics slow gastric emptying, so low-dose tricyclics or gabapentin are probably safer. Acupressure, acupuncture, ginger, and hypnotherapy have also been suggested, although Lacy pointed out that symptoms "can wax and wane," so one must be careful about unconfirmed reports.

Several surgical approaches have been used. Venting gastrostomy and combination gastrostomy and jejeunostomy may be reasonable for patients with severe antral hypomotility or pylorospasm, although studies of these approaches are retrospective and uncontrolled. Lacy reviewed his study of eight type 1 diabetic patients administered botulinum toxin by injection during upper endoscopy into the pylorus, with symptoms improving substantially; this result requires verification in a controlled trial (15). A number of studies have assessed the usefulness of high-frequency low-energy gastric stimulation with surgically implanted elec-

trodes (16), with one relatively large study of 33 patients showing that approximately half had substantial improvement in nausea and vomiting (17).

At a study presented at the ADA meeting, Karatzidou et al. (abstract 5) performed laparoscopic implantation of a gastric high-frequency electrical stimulation device in nine type 1 diabetic individuals with symptoms of refractory gastroparesis, finding a reduction in A1C from 10.3 to 8.3% over 6 months and reduction in the standard deviation of interstitial glucose measured with continuous glucose monitoring, suggesting improvement in mean glucose and in glycemic variability. It should be noted, of course, that such a glycemic improvement might in itself improve what initially appeared to represent intractable gastroparesis.

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