# The 32nd Annual Meeting of the European Association for the Study of Diabetes

## Neuropathy, health care, and glycation

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This is the second of four reports on the 1996 meeting of the European Association for the Study of Diabetes (EASD), which was held in Vienna, Austria, in September.

### Neuropathy

A number of presentations at the meeting dealt with neuropathy. D. Ziegler et al., Düsseldorf, Germany, reported an association of increased levels of diabetic neuropathy with poor glycemic control during a 10-year prospective study (124; references in parentheses are to abstract numbers from the Abstracts of the 32nd Annual Meeting of the European Association for the Study of Diabetes, *Diabetologia* 39 [Suppl. 1]:A1–A310). Other investigators presented data on diabetic foot disease and gastrointestinal neuropathy.

Diabetic foot disease was discussed by K.P. Bouter et al., Utrecht, The Netherlands (5). In a 5-year follow-up of 259 patients hospitalized for diabetic foot lesions, it was found that 37% of patients were readmitted for further foot lesions within 1 year and 56% within 2 years. Overall mortality was 46% and 60% at 1 or 2 years, and this was associated with myocardial infarction in 28%, stroke in 11%, and infections arising from the foot in 19%. C. Vermigll et al., Manchester, U.K. (1000), reported a 61.7% prevalence of foot deformity in 666 patients with diabetes, including small muscle wasting, hammer/claw toes, prominent metatarsal heads, Charcot's foot, and limited joint mobility. Forty patients had ulcers at the time of the study or had had them previously. These were not related to foot deformity but showed significant association with neuropathy. However, J.J.J. de Sonnaville et al., Amsterdam, The Netherlands (999) studied pre-ulcerative lesions in 609 patients with type II diabetes. Fifteen percent had feet that were insensitive to the 10-g Semmes-Weinstein monofilament, 56% lacked ankle reflexes, and 18–23% had decreased ankle-brachial blood pressure ratio. Pre-ulcerative lesions were found in 12.9% of the patients and were significantly associated with diabetes duration, cigarette smoking, decreased ankle-brachial blood pressure index, insensitive feet, dry feet, and hammer-toe deformation.

Gastrointestinal autonomic neuropathy was discussed by M. Horowitz, Adelaide, Australia, who presented data on gastric emptying and recalled Mark Twain's aphorism, "To eat is human, to digest, divine!" Scintographic techniques show delayed gastric emptying in 30–50% of patients with long-standing diabetes, although the frequency may be less when measured while euglycemia is maintained. It is important to measure emptying of both solid and liquid test meals, preferably simultaneously, because there is only a modest correlation between these. Patients with early diabetes appear to have more rapid gastric emptying in some studies, but not in Horowitz's own work. There is a significant but relatively weak correlation between cardiovascular autonomic neuropathy and delayed gastric emptying. Hyperglycemia slows gastric emptying, which suggests that there is a reversible component. This phenomenon can be shown even within the physiological range of blood glucose, from 4 to 8 mmol/l, in diabetic and nondiabetic subjects. Furthermore, hypoglycemia accelerates gastric emptying. Hyperglycemia also slows transit from the duodenum to the cecum, so it appears that glucose is a physiological regulator of overall gastrointestinal function. Reviewing the physiology of gastric emptying, Horowitz pointed out that it occurs in intermittent pulses and that gastric contractions are controlled by a pacemaker in the fundus with an electrical activity of 3 discharges/min, although not all of these discharges initiate gastric contraction. Jejeunal receptors feed back to the stomach to regulate gastric emptying. Dietary glucose supplements given to nondiabetic subjects increase gastric emptying. Possible mechanisms of the delayed gastric emptying in patients with diabetes include decreased gastric contractile force and disordered contractions. Horowitz's data show the latter to be the predominant mechanism. Irregularity of the gastric pacemaker rhythm, "the equivalent of ventricular fibrillation of the stomach," is associated with hyperglycemia, which also stimulates pyloric contraction and thus further delays gastric emptying. A recent study showed that hyperglycemia actually suppresses peak blood levels of glipizide after oral doses, further emphasizing the important effects of gastric emptying on diabetes treatment. Other factors, such as gastric disease and smoking, also delay gastric emptying. All of these must be assessed in the patient with diabetes who complains of gastrointestinal symptoms.

Gastrointestinal symptoms experienced by patients with diabetes include loss of appetite (16%), early satiety (26%), and postprandial "fullness" (20%). These symptoms occur more frequently in women than in men and are associated with higher $HbA_{1c}$ levels, but they are only weakly correlated with delay in gastric emptying. Other explanations for such symptoms include the effect of blood glucose itself, psychological factors, and other gastrointestinal pathology. Patients with diabetes are more prone to the development of nausea during gastric distention or with duodenal triglyceride infusion, and both of these tendencies can be duplicated in nondiabetic subjects by infusing glucose to produce similar levels of hyperglycemia. An interesting study by A.F. Celik et al., Istanbul, Turkey (1185), compared 250 patients with

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diabetes with 250 nondiabetic subjects. By a variety of measures, constipation was 1.5- to 2.0-fold more common in patients with diabetes, whereas the frequency of diarrhea was similar, which suggests that the former may be a neuropathic manifestation.

In patients with type I diabetes, postprandial fullness is more than twice as common with hyperglycemia. Delay of gastric emptying leads to a smaller rise in blood glucose after a meal, and pramilitide, an amylin analog, slows the rise in blood glucose postprandially. Pramilitide has therefore been advocated as a means to improve glycemic control, although in view of the above cited factors, it can be used only sparingly in people with diabetes, many of whom already have delays in gastric emptying. More to the point is the need to optimize the coordination between gastric emptying and insulin in patients with type I diabetes, and patients with type II diabetes probably benefit from slowed gastric emptying and gastrointestinal transit, which accounts for the benefit of fiber supplementation.

Treatment of gastroparesis includes the use of prokinetic drugs that cause dopamine receptor blockage, such as metoclopramide (which, however, has central nervous system side effects) and domperidone. Also used are motilin agonists such as erythromycin, which is the most potent agent, at least when administered parenterally in short-term studies, and cisapride, which Horowitz termed the best-tolerated drug. Cisapride is also the only one of these drugs for which long-term efficacy has been established, although Horowitz remarked that synergy between this and other agents deserves further study. He stressed that gastric emptying should be measured before and during treatment.

A number of agents are being investigated for the overall treatment of neuropathy. We should still regard the aldose reductase inhibitors as having therapeutic potential, and D.A. Greene et al., Ann Arbor, MI, Bronx, NY, and Groton, CT (122), showed evidence that zopolrestat improves several electrophysiological parameters of neuropathy. In terms of treatment of pain, A. Quatraro et al., Naples, Italy (991), compared calcitonin nasal spray, 100 units daily, and acetyl-l-carnitine, 500 mg b.i.d., given to 20 patients with painful neuropathy and type II diabetes. Both agents decreased symptom score on a 0–10 visual analog scale, from 7.6 to 5.1 with calcitonin and from 7.3 to 3.2 with the carnitine preparation. However, M. Rejanovic et al., Zagreb, Croatia (989), reported in a randomized crossover 6-week controlled trial of 60 patients that mexilitine at a dose of 450 mg/day showed no greater benefit for painful diabetic neuropathy than a placebo.

Lipoic acid received a great deal of attention at the EASD meeting. P.A. Low et al., Rochester, MN, and Frankfurt, Germany (120), and F.A. Gries et al., Düsseldorf, Frankfurt, Zwickau, and Bochum, Germany (121), showed in animal and human (800 mg/day) studies, respectively, that α-lipoic acid decreased electrophysiological parameters of neuropathy. T. Haak et al., Frankfurt, Germany (990), reported a beneficial effect of α-lipoic acid at a dose of 1,200 mg/day on nail bed capillary blood cell velocity, temperature discrimination, and vibration sensitivity. There may also be a glucose-lowering action. M. Khamaisi et al., Beer-Sheva, Israel (528), gave 100 mg/kg lipoic acid intravenously to fasting rats and reported a fall in glucose from 68 to 35 mg/dl at 1–2 hours in normal rats and from 373 to 184 mg/dl at 8 hours in streptozotocin-induced diabetic rats. The effect did not occur postprandially, and the hepatic response to 20 μg/kg glucagon was abolished, suggesting an effect on gluconeogenesis. Another possible effect of lipoic acid seen in other studies is increased muscle GLUT4. In a study on humans, T. Konrad et al., Frankfurt, Germany, and Padova, Italy (859), administered lipoic acid at a dose of 600 mg twice daily to 10 lean and 10 obese patients with type II diabetes and found evidence of decreased glucose levels.

## Health Care

A number of studies presented at the meeting addressed issues of health care and the cost of treatment. For example, H.B. Mortensen and P. Hougaard for the Hvidøre Study Group on Childhood Diabetes, Copenhagen, Denmark (100), discussed results of a cross-sectional investigation of 2,873 patients from 22 pediatric departments in North America, Europe, and Japan. The mean $HbA_{1c}$ of these patients, measured at a central laboratory, was 8.6 ± 1.7% (normal range, 4.4–6.3%). Insulin was administered twice daily to 59% and three times daily to 37% of the patients. T. Valle et al., Helsinki, Finland (101), assessed glycemic control in a randomly selected sample of 3,800 patients from throughout the country. Mean age was 58, and mean duration of diabetes was 11 years. Mean glycohemoglobin concentration was 8.6% (normal 4–6%), although it had been measured in only 67% of patients. Of the patients studied, 13% were treated with diet alone, with a mean glycohemoglobin concentration of 6.5%; 37% with oral agents, with a mean glycohemoglobin concentration of 8.3%; 39% with insulin, with a mean glycohemoglobin concentration of 8.8%; and 11% with both insulin and oral agents, with a mean glycohemoglobin concentration of 9.5%. The authors of both studies concluded that there is room for improvement in the treatment of patients with diabetes.

K.A. Javor et al., Indianapolis, IN (757), studied costs of medical care among 238 patients with type I diabetes. Of these patients, 72 had 163 episodes of ketoacidosis, each costing $6,416, which represents 25% of health care costs for all the patients. Those patients with ketoacidosis had an average annual medical charge of $13,152 vs. $5,570 for patients not experiencing ketoacidosis. The 24 patients with multiple episodes were responsible for 70.5% of ketoacidosis episodes, representing 16% of all medical charges for the patients. Before ascribing this to purely medical characteristics of patients, we should note a fascinating assessment of the role of psychosocial factors in outcome among patients with type I diabetes reported by J. Östman et al., Stockholm, Uppsala, and Umeå, Sweden (104). These researchers reviewed mortality among 4,115 patients with diabetes developing between ages 15 and 33 and entered in a central registry between 1983 and 1992. Of 58 deaths, 11 were associated with hyperglycemia and 7 with hypoglycemia. Twenty-one deaths were associated with excessive alcohol use, 4 with abuse of other drugs, and 7 with "mental insufficiency," and 8 were suicides, leaving only 18 without psychological factors. W. Rathmann et al., Düsseldorf, Germany, Frankfurt, Germany, and Birmingham, AL (737), reviewed computerized data from 1994 on drug prescriptions for 386,520 people, of whom 30,558 had diabetes. Of those people with diabetes, 20% were treated with insulin and 45% with oral agents. Controlling for age, sex, and the physician's specialty of practice, patients with diabetes showed increased rates of treatment with loop diuretics (odds ratio 2.7), digoxin (2.5), ACE inhibitors (2.5), nitrates (1.9), thiazides (1.8), $Ca^{2+}$ channel blockers (1.8), fibrates (2.5), gout medica-

tions (1.9), and wound-care products (1.4). Decongestants, "flu medicine," migraine drugs, and muscle relaxants were prescribed less frequently. There was no increase in rates of treatment with a variety of other drugs, including thyroid hormone and vaccines. Overall, 33% of diabetic patients but only 12% of nondiabetic patients received more than 10 different drug prescriptions per year.

An optimistic report was offered by M.P. Lanti et al., Rome, Italy (765), who assessed 2,053 employed individuals from a population of 5,011 people with diabetes. Only 13.8% of diabetic men and 10.6% of diabetic women had experienced modification of their jobs, and for the majority (77.5% and 84.2%) these modifications were at the suggestion of employers. Finally, A. Nicolucci et al., Chieti, Italy, Perugia, Italy, and Alexandria, Egypt (766), used regression analysis to show that poor control of hypertension was associated with a 3.1-fold increase in risk of complications, poor clinic attendance was associated with a 1.7-fold increase, and lack of diabetes education increased complications 4.1-fold. They used this assessment to suggest that 39% of the burden of diabetes complications might be reduced by intervention in these three areas alone.

## Glycation

Another topic addressed at the meeting was the role of glycation in diabetes. H. Vlassara, Manhasset, NY, spoke on advanced glycation end product (AGE) receptors and diabetic complications. "We used to think," she explained, "that late glycation occurs only on proteins that have a long half-life. This is not true." She described the presence of AGEs on proteins with a half-life of only 4–6 weeks, including a wide variety of proteins from intracellular organelles and extracellular proteins. "We are talking about hundreds or thousands of compounds turning over constantly," she continued, emphasizing that two different characteristics of AGEs are relevant to the pathophysiology of diabetes. First, AGEs are found in macromolecules and covalently cross-link with other amino groups, causing, for example, the increased collagen cross-linking associated with diabetes. The second, and more recently appreciated, characteristic is the binding of AGEs to specific sites on a variety of proteins, including lysozyme and lactoferrin, which is a phenomenon seen principally on cells of the reticuloendothelial system, including macrophages, endothelial cells, fibroblasts, and smooth muscle cells. The apparently similar binding sites include those on galectin-β and the receptor for AGE (RAGE), both of which have 18 amino acid residues with cysteine at either end but otherwise show no homology. These binding sites are different from those of the scavenger cell receptor system, which is limited to the macrophage and monocyte and is able to clear oxidatively modified molecules. Some of these AGE binding sites may actually show downregulation by insulin. Binding to these sites may activate cytokines or trigger oxidative stress, and a given protein may have AGEs in various stages of development, some of which are inert and cross-linked and others of which are highly reactive. Vlassara stressed the importance of renal AGE clearance and the increased AGE levels that result from renal insufficiency. She went on to discuss the potential benefits of aminoguanidine, which prevents AGE formation, although this agent does not interfere with interaction of already formed AGEs with receptor sites. She speculated on whether AGEs may have a role in development, in remodeling, or in stimulation of further growth. "Really," she said, "one wants to think that there is a wisdom of the system for replenishing, replacing, and also repairing, although with increased exposure toxic events are expectable."

Among the other reports on glycation presented at the meeting was that of S. Yamagishi et al., Kanazawa, Japan (196), who showed that AGEs retard retinal pericyte growth and are cytotoxic to pericytes through interaction with RAGE. AGE may be thrombogenic because of effects on endothelial prostacyclin production and may also upregulate vascular endothelial growth factor, leading to angiogenesis. F. Pricci et al., Rome, Florence, and Cantanzaro, Italy, and Manhasset, NY (80), reported that mesangial IGF and transforming growth factor-β synthesis is increased by glucose-modified proteins via an AGE receptor–mediated mechanism. S. Youssef et al., West Heidelberg, Australia (81), showed evidence of low-affinity specific AGE binding sites in diabetic rat kidney. T.J. Borg et al., Oslo, Norway, and Manhasset, NY (258) showed that AGEs are increased in serum of children with type I diabetes. T. Kochinsky et al., Düsseldorf, Germany, and Manhasset, NY (257), presented data indicating that AGEs are absorbed from a variety of cooked foods and may contribute to diabetic complications. They reported decreased clearance in patients with micro- as well as macroalbuminuria. A. Festa et al., Vienna, Austria (523), showed an association between increased levels of specific AGE receptors on monocytes and higher levels of $HbA_{1c}$ in patients with type I diabetes and poor glycemic control, and H.J. Baumgartl et al., Munich, Germany, and Manhasset, NY (1111), reported that serum AGE levels were 16.9 U/ml in patients with type I diabetes who smoked vs. 11.4 U/ml in nonsmokers. There was an acute 5 U/ml increase in AGE levels after subjects smoked two cigarettes. Finally, in what one hopes will augur the development of new therapeutic approaches, K. Katsuno et al., Matsuno, Japan (524), showed data on two non-hydrazine compounds that are 10 times as potent as aminoguanidine in inhibiting AGE formation in vitro. These compounds appear to act at different steps than aminoguanidine, so presumably combined treatment would reduce AGE formation even further.