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Nephropathy and neuropathy

ZACHARY T. BLOOMGARDEN, MD

This is the sixth of eight reports on the American Diabetes Association (ADA) Annual Meeting and Scientific Sessions held in San Diego, California, in June 1999. It covers topics related to the assessment and treatment of diabetic nephropathy and neuropathy, focusing in particular on recent studies of diabetes-related hypertension, lower-extremity ulceration, peripheral neuropathy, and erectile dysfunction.

Hypertension

Lennart Hansson, Uppsala, Sweden, gave an update on the outcome of hypertension treatment in diabetes. The frequency of cardiovascular disease (CVD) is two to three times higher among patients with diabetes versus patients without diabetes (1), and data compiled by the World Health Organization show that CVD is a major cause of death (2). According to the Multiple Risk Factor Intervention Trial study, the frequency of CVD-related mortalities was three- to fourfold higher among patients with diabetes, regardless of their blood pressure levels; in particular, diabetic patients with low blood pressure levels appeared to be at an increased risk for hypertension (3). Normal blood pressure measurements are considered to be <130/85 mmHg, and optimal blood pressure measurements are considered to be <120/80 mmHg. In total, there are ~50 million people in the U.S. who are hypertensive. Blood pressure levels are well controlled in only 27% of U.S. patients. Effective control of blood pressure levels is less frequent in Western Europe (only an estimated 6% of U.K. patients have good blood pressure control), and effective hypertension control in the developing world is even less frequent than that in Western Europe (4). The fourth report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommended the use of diuretics and β-blockers as the first-line treatment for all patients, the use of calcium-channel blockers (CCBs) for elderly patients, and the use of ACE inhibitors (ACEIs) for patients with diabetes. Other first-line agents are α-blockers and angiotensin II receptor blockers (ARBs). The Hypertension Optimal Treatment Study consisted of 19,000 patients who were randomized to achieve diastolic blood pressures of 90, 85, and 80 mmHg. All of the study patients received aspirin. The risk of a major CVD-related incident decreased by 30% in the nondiabetic patients. Of the 1,501 patients with diabetes, 24, 18, and 11 patients of the 3 treatment groups, respectively, experienced major CVD-related incidents, resulting in a risk reduction of 37% in the lowest blood pressure group (5). In the hypertension substudy of the U.K. Prospective Diabetes Study (UKPDS), 1,148 patients with hypertension were randomized to “tight” blood pressure control with ACEIs or β-blockers or to “less tight” control, with an average blood pressure reduction of 10/5 mmHg with tight control. The intervention group experienced a 32% decrease in the prevalence of diabetes-related deaths, a 44% decrease in the prevalence of stroke, a 37% decrease in the prevalence of cardiovascular disease, and a 56% decrease in the prevalence of heart failure (6). The Captopril Prevention Project evaluated 11,000 patients who were treated with either ACEIs or β-blockers plus diuretic treatment and showed similarly that both treatments are equally effective, using at a somewhat higher blood pressure goal than that of the UKPDS tight blood pressure control group. However, among the 700 patients with diabetes in the study, ACEI treatment decreased rates of myocardial infarction (MI), total CVD, and mortality (7). Interestingly, the incidence of diabetes was 9% lower in the nondiabetic patients who were randomized to ACEIs; this finding suggests that either use of this treatment has beneficial effects or that the use of β-blocker-diuretic combination treatment has adverse effects. In the Systolic Hypertension in Europe study, 4,900 patients with systolic hypertension showed benefit of treatment with nitrendipine (8). Of these patients, ~10% had diabetes and showed somewhat greater benefit of treatment (9).

Dalila Corry, Sylmar, CA, discussed the renal protective effects of ACEIs and CCBs, commenting that “we are no longer so sure if the ACEI[s] are the mainstay of protection.” Parving et al.’s (10) studies in the 1980s showed that blood pressure control slows the decline in the glomerular filtration rate (GFR) from 0.9 to 0.3 ml · min⁻¹ · m²⁻¹. Anderson and Brenner (11) subsequently showed particular benefit of ACEI treatment in animal models. Subsequent clinical studies showed a 50% decrease in renal function loss with ACEI treatment (12). Meta-analysis of ACEI treatment shows that these effects are independent of the decrease in blood pressure, the type of diabetes, or the stage of nephropathy (13). ACEIs improve insulin sensitivity, and they have intrarenal effects that include...
afferent arterial constriction with efferent arteriolar dilation, which decreases the transglomerular pressure differential. The decrease in local angiotensin II (A2) may also decrease tubular sodium reabsorption, endothelial transforming growth factor (TGF)-β, platelet-derived growth factor (PDGF), and mesangial matrix production. In angiotensinogen-knockout mice, the glomerular size and GFR decrease (14). Such animals can be seen as a model of ACE polymorphism, a phenomenon that may explain differing responses to ACEIs in the population: patients with the D/D phenotype are more sodium- and diuretic-responsive, whereas those patients with the I/I and I/D phenotypes show little response (15). Bradykinin and A2 both play a role in blood pressure control by reporting the effects of ACEIs, but, because of non-ACE generation of A2, there may be escape from the effects of these agents, which can be treated with ARB, although clinical data are not yet definite. Nifedipine and diuretics may be of less benefit in preventing nephropathy. CCBs are effective blood pressure treatment agents that increase glomerular membrane selectivity and decrease tubular damage from proteinuria (16). Comparison of nisoldipine with lisinopril in an antihypertensive treatment of diabetic patients shows a smaller decline in the GFR and levels of albuminuria (17), whereas comparison of using amlodipine with cilazapril resulted in similar declines in blood pressure levels, albuminuria levels, and the GFR (18). Corry concluded that combination treatment regimens that incorporate both classes of treatment may prove useful, particularly for patients with proteinuria who aim to achieve blood pressure levels <125/75 mmHg.

Tomlinson and Close (abstract 607) described the difficulty of achieving effective blood pressure control by reporting the responses to stepped antihypertensive treatment with a converting enzyme inhibitor, a thiazide-loop diuretic, a β-blocker, a CCB, and, finally, an α-blocker in 40 patients with nephropathy and a mean initial blood pressure of 170/88 mmHg (abstract numbers refer to the Abstracts of the 59th Annual Meeting and Scientific Sessions of the ADA, Diabetes48 [Suppl. 1]:A1-A550). A blood pressure level <130/85 mmHg was achieved in only six patients. Only 23 patients achieved a diastolic blood pressure level <85 mmHg, and, despite treatment with all five agents, 11 failed to achieve a blood pressure level <130/85 mmHg. Kazumi et al. (abstract 1664) reported the results of a 2-year follow-up of 436 patients with type 2 diabetes and hypertension with or without microalbuminuria who were treated with nifedipine retard versus enalapril. The mean urinary albumin excretion rate (AER) increased similarly from 45 to 64 mg/day and from 42 to 74 mg/day with a similar risk of acute MI, anginapectoris, and stroke of 2.1 vs. 3.5%, respectively. In another study that compared CCBs with ACEIs, Baines et al. (abstract 152) randomized 50 normotensive patients with type 1 diabetes who had a mean level of albuminuria of 148 µg/min (range 25-1,599) to enalapril 10 mg a day vs. nifedipine retard 20 mg daily vs. placebo. Albuminuria levels decreased with enalapril only, and none of the treatments changed the mesangial volume fraction, mean glomerular volume, filtration surface, glomerular basement membrane width, or percentage of occluded glomeruli over the course of 3 years. Adler et al. (abstract 63) reported the estimated risks of diabetic complications associated with systolic blood pressure in 3,642 individuals aged 25-65 years with newly diagnosed type 2 diabetes from England, Scotland, and Northern Ireland, who were enrolled in the UKPDS and followed for a median 10.4 years. Each 10-mmHg increase in systolic blood pressure increased the relative risk of MI by 13%; that of stroke by 23%; that of diabetes-related death by 20%; and that of any microvascular complication, mostly due to retinal disease, by 15%. Incidents of MI and stroke occurred annually in 3.6 and 1.6% of those patients with systolic blood pressure >160 mmHg. Cruickshank et al. (abstract 501) reported that to prevent 1 retinal or renal end point in the UKPDS, 138 patients needed to be treated for 1 year with tight control of hypertension, as compared with 357 patients treated with tight glycemic control, with the number-needed-to-treat to prevent any diabetes end point being 61 vs. 196. These findings suggest that target organ damage in diabetes could be regarded as blood pressure-dependent on a permissive background of hyperglycemia and hyperlipidemia. Valdez and Narayan (abstract 64) reported on the 1995 and the 1997 Behavioral Risk Factor Surveillance System, a population-based telephone survey of 249,516 individuals aged >18 years. Among those with and without diabetes, 39.0 and 15.5% of non-Hispanic Caucasians, 52.8 and 23.5% of non-Hispanic African-Americans, and 33.3 and 14.1% of Hispanics reported as having hypertension; diabetes conferred a 2.1-, a 3.1-, and a 2.3-fold increase in the risk of hypertension in the three ethnic groups, respectively. Both hypertension and diabetes affected 0.4, 3.1, and 5.4% of non-Hispanic Caucasians aged 18-44, 45-64, and ≥65 years, respectively. The corresponding prevalences were 0.9, 10.0, and 13.7% among non-Hispanic African-Americans and 0.6, 5.5, and 8.9% among Hispanics. Malik et al. (abstract 287) reported that resistance vessels from gluteal fat biopsies of 24 patients with type 1 diabetes (mean duration 25 years) showed correlation of endothelium-dependent relaxation produced by acetylcholine with HbA1c levels, similar norepinephrine-induced vasoconstriction to that of control subjects, and greater A2-induced vasoconstriction than that of control subjects. These findings may explain the enhanced benefits of using ACEIs to treat diabetes. Genetic factors may explain particular benefits of ACEI treatment in certain patients. Hadjadj et al. (abstract 153) followed 310 patients with type 1 diabetes for 6 years to evaluate the role of ACE I/D polymorphism in the development of diabetic nephropathy. Of these patients, 54 had the I/I genotype, 149 had the I/D genotype, and 106 had the D/D genotype. Their results showed that 2 I/I patients progressed in nephropathy with an 11.5-fold greater progression of 32 I/D and 16 D/D patients. The protective effect of the I/I genotype was seen also in the 251 patients without nephropathy at baseline, independent of both the 32% increase in risk for each 1% increase in HbA1c value and the 4% increase in risk for each 1 mmHg increase in systolic blood pressure. Casartelli et al. (abstract 575) reported that in 79 patients with type 2 diabetes, the D/D genotype was present in 46% of those patients with coronary heart disease (CHD) and in only 20% of those patients without CHD. However, their results did not show a significant association between genotype distribution and detection of nephropathy. Taniwaki et al. (abstract 572) found that in 137 patients with type 2 diabetes, the D allele of ACE gene polymorphism was associated with increased carotid artery intima- medial thickness, regardless of non-HDL cholesterol levels.

Nephropathy
Studies presented at the ADA Annual Meeting suggested that mediators of nephropathy include prostanoid and E2, mitogen-activated protein kinase (MAPK), islet amyloid
polypeptide (IAPP), atrial natriuretic peptide (ANP), PDGF, glycated albumin, and TGF-β. Ishibashi et al. (abstract 148) showed that hyperglycemia increases specific prostaglandin E receptors and increases prostaglandin E2 production, and that it potentially plays a role in increasing mesangial cell DNA synthesis and hyperglycemia of early nephropathy. Wilmer and Dixon (abstract 154) cultured human mesangial cells with high glucose concentrations, and Dlugosz et al. (abstract 592) cultured similar cells under conditions mimicking the effect of hypertension, showing protein kinase C (PKC)-independent activation of p38 and p44/p42 MAPK, which could potentially mediate the structural changes of diabetic nephropathy. IAPP mRNA is present in fetal rat kidney, but it disappears shortly after birth. Abrass et al. (abstract 155) found IAPP-immunostaining in the abnormal mesangial matrix in four of five rats with streptozotocin-induced diabetes and in four of eight humans with type 2 diabetes; IAPP-immunostaining was not found in rat or human nondiabetic control subjects. They also found IAPP mRNA in cultured mesangial cells by use of polymerase chain reaction. Expression of IAPP mRNA increased when incubated at higher glucose concentrations. Suggesting potential hormonal mediators, McKenna et al. (abstract 589) showed that intravenous infusion of brain natriuretic peptide and ANP increases the urinary AER ~10-fold in normoalbuminuric individuals with type 1 diabetes. Cohen et al. (abstract 616) showed that glycated but not nonglycated albumin increased cultured rat glomerular endothelial cell PKC activity with increased collagen IV production, and demonstrated that this effect could be prevented by a PKC inhibitor. Yokota et al. (abstract 149) used a PDGF-β receptor-selective inhibitor, Ki6896, which inhibits autophosphorylation of PDGF-β receptor, to show that the effect of hyperglycemia in the expression of TGF-β in mesangial cells was decreased by the inhibitor and could be mimicked by incubation with PDGF. The inhibitor may have therapeutic benefits. Krag et al. (abstract 614) created a transgenic mouse with localized renal TGF-β1 overproduction to investigate the effects of TGF-β1 on kidney function. Their results showed glomerular and tubular dysfunction with decreased urinary concentration ability, increased urine flow rates, decreased GFRs, and increased urinary AERs. However, Cummings et al. (abstract 605) studied 156 children with type 1 diabetes for 5–10 years and 44 nondiabetic control subjects. Excretion rates of urinary TGF-β1 were increased in the diabetic patients and were associated with the onset of puberty and with kidney volume. They were not, however, associated with albuminuria or HbA1c levels, which indicates that increased levels of TGF-β1 are only partially related to diabetic nephropathy.

A number of clinical studies of nephropathy were presented. Florkowski et al. (abstract 186) compared patients who were diagnosed with type 1 diabetes in 1970–1976 with patients who were diagnosed in 1977–1983. The cumulative 25-year nephropathy incidence was 41 vs. 25%, respectively, despite similar 10-year retinopathy rates of 23 and 29% and mean HbA1c levels of 7.7 and 7.9%. Such data suggest that nonglycemic factors, such as improved blood pressure treatment, played a role in decreasing the prevalence of nephropathy. Schultz et al. (abstract 595) followed 287 children with type 1 diabetes for >4.5 years from the time of onset. The prevalence of microalbuminuria was 40% at 11 years of age. Factors such as sex, duration of diabetes, onset of puberty, and glycemic levels were associated with the detection of microalbuminuria. The prevalence of microalbuminuria increased by 36% for every 1% increase in HbA1c values. White et al. (abstract 602) performed renal biopsies on 21 patients with type 2 diabetes and macroalbuminuria, showing that the mesangial volume positively correlated with the level of proteinuria and negatively correlated with the creatinine clearance rate and blood pressure levels; these patterns are similar to those in patients with type 1 diabetes. Earle et al. (abstract 606) studied 10 Asian European, 11 African-European, and 24 Caucasian patients with type 2 diabetes and showed that those patients of Asian ancestry had a greater tendency to develop nephropathy and experienced less the renoprotective effects of ACEIs. Walker et al. (abstract 618) followed 1,550 insulin-treated patients for 4 years. The risk of retinopathy was increased at a baseline urinary albumin concentration >55 mg/dl, and the risk of nephropathy was associated with a baseline urinary albumin concentration >7.4 mg/dl. These findings suggest that intervention with ACEIs may be justifiable at much lower levels than those that are currently used. However, Lawson et al. (abstract 625) analyzed six studies of 14–249 adolescents with type 1 diabetes who were followed for 3–10 years and found that 46% of those patients with microalbuminuria at baseline became normoalbuminuric (<20 µg/min) and only 16% developed macroalbuminuria (>200 µg/min) without treatment. Therefore, the use of ACEIs may not be needed for all microalbuminuric adolescents. Girelli et al. (abstract 635) reported on 2,410 patients with type 2 diabetes who were treated from 1990 to 1998. Retinopathy and hypertension, respectively, were seen in 17 and 33% of those with normoalbuminuria, in 28 and 42% of those with microalbuminuria, and in 49 and 52% of those with macroalbuminuria. Ischemic heart disease developed in 11% of those with normoalbuminuria and in 17 and 19% of those with micro- and macroalbuminuria. Similarly, Arauz-Pacheco et al. (abstract 585) reported that of 312 Native Americans with type 2 diabetes, 42% had albumin-to-creatinine ratios >30 with a 27 vs. 11% prevalence of ischemic heart disease, as compared with those patients with albumin-to-creatinine ratios <30. Those patients who also had LDL cholesterol levels >160 had a 53% prevalence of ischemic heart disease, which attests to the importance of conducting multiple risk factor assessments. Nanni et al. (abstract 783) reported that the A1 allele of the Scal polymorphism of the human ANP gene, which is associated with lower plasma ANP levels and with preserved day-to-night blood pressure changes, was less frequent in patients with type 1 diabetes who developed macroalbuminuria. This finding suggests that Scal polymorphism of the ANP gene protects against nephropathy. Velussi et al. (abstract 1657) reported that in type 1 diabetic patients with creatinine levels <1.5 mg/dl, 12.4% of 710 women with normoalbuminuria, but 24.6% of 342 women with microalbuminuria, had hemoglobin levels <13 g/dl. In a similar number of men with serum creatinine levels <1.5 mg/dl, 2.3 and 5%, respectively, had hemoglobin levels <13 g/dl. Therefore, microvascular disease in the peritubular renal interstitium, where erythropoietin-secreting cells are located, may lead to anemia.

Neuropathy

Fascinating information regarding aldose reductase inhibitors (ARIs) that further suggested that they will potentially play a clinical role in the treatment of diabetic nephropathy was also presented at the ADA meeting. Nakamura et al. (abstract 228) treated streptozotocin-induced diabetic rats with the PKC-β-specific inhibitor LY-333531 and the ARI NZ-314, separately...
and in combination. Motor nerve conduction velocity (MNCV) was decreased by one-third in those rats with diabetes, but there was a 50% restoration of MNCV by use of combination treatment; however, there was no significant restoration of MNCV with use of either treatment alone. In addition, sciatic nerve blood flow (NBF) was decreased by two-thirds in the diabetic rats, but there was a 50% restoration with the use of LY-333531, and the rate of sciatic NBF returned to normal by use of combination treatment; use of ARI treatment alone showed no benefit. Another study of combination treatment by Cameron et al. (abstract 656) showed a synergistic interaction between the ACEI lisinopril and the ARI ZD5522 (Zenea Pharmaceuticals, Wilmington, DE). In streptozotocin-induced diabetic rats, each agent restored MNCV by 20%, whereas the combination treatment corrected nerve conduction to that of control levels. Similarly, there was minimal increase in sciatic NBF with either agent alone, but there was almost complete normalization with combination treatment. Song et al. (abstract 283) showed that Schwann cell-specific overexpression of aldose reductase in transgenic mice, as compared with that in nontransgenic mice, worsened diabetic and galactosemic neuropathy with only a small additional sciatic nerve accumulation of sorbitol or galactitol, respectively. These findings indicate that levels of sorbitol or galactitol may not underlie nephropathy-associated hyperglycemia and galactosemia. Rather, the depletion of NADPH caused by increased flux through the polyol pathway during hyperglycemic or galactosemic states mediates the adverse effects on nerve function. This hypothesis was supported by Ido et al. (abstract 650), who studied the effect of inhibitors of sorbitol dehydrogenase and aldose reductase reverse on rats that had untreated streptozotocin-induced diabetes for 6 weeks, during which MNCV had decreased by 14%. After 2 weeks, the sorbitol dehydrogenase inhibitor group experienced an 11% decrease, and the ARI group experienced a 5% decrease in MNCV. After 4 weeks of treatment, MNCV returned to normal levels in both groups. Sciatic NBF decreased by 19% in the untreated group and by 14% in the sorbitol dehydrogenase inhibition group at 4 weeks; in the ARI-treated group, though, sciatic NBF returned to normal. As compared with control levels, nerve sorbitol levels in the three groups were increased by 12-, 61-, and 0.35-fold, respectively, at 4 weeks, but fructose levels were increased by 7-fold in the untreated group and were normalized in both treatment groups. These data suggest that sorbitol metabolites, and/or metabolic imbalance from increased oxidation of sorbitol to fructose, mediate the impairment in nerve function in early diabetes, and that early diabetes-related nephropathy is not a result of elevated levels of sorbitol per se.

Ferreira et al. (abstract 7) showed that acute streptozotocin-induced diabetes decreases rat sciatic nerve lipoprotein lipase expression in adipose tissue, heart, and soleus muscle. Because lipoprotein lipase levels decrease in diabetes and because the enzyme plays a role in peripheral nerve phospholipid synthesis, lipoprotein lipase may be involved in the pathophysiology of diabetic neuropathy. Orobosova et al. (abstract 229) administered the α₁-adrenoceptor antagonist prazocin to rats with streptozotocin-induced diabetes. Administration of prazocin prevented the decrease in NBF and MNCV and resulted in improved measurements of mitochondrial oxidative capacity and tissue oxygenation. These findings further support the rationale for using vasodilator therapy to treat diabetic neuropathy. Cameron et al. (abstract 230) administered the iron chelator deferoxamine to streptozotocin-induced diabetic rats after 6 weeks without treatment. Administration of deferoxamine restored nerve conduction and blood flow. Packer et al. (abstract 649) reported that the sciatic nerve content of α-lipoic acid, an antioxidant and cofactor of several enzyme complexes that regulate mitochondrial energy metabolism, can be increased in a dose-dependent fashion in a rat model by oral feeding.

In clinical studies of ARI, Johnson et al. (abstract 574) studied 88 patients with diabetic cardiomyopathy. Diabetic cardiomyopathy was by a low-peak filling rate or subnormal excretional increase in ejection fraction by radionuclide ventriculography in the absence of either coronary artery disease on stress thallium imaging or left ventricular hypertrophy on an echocardiogram. After 1 year of treatment with the ARI zopolrestat, as compared with placebo, systolic function improved, which suggests that zopolrestat could play a role in treating diabetic patients with congestive heart failure and low ejection fractions. Didangelo et al. (abstract 651) treated 45 patients with diabetic autonomic neuropathy with the ARI tolrestat or placebo for 1 year. After administration of tolrestat, heart rate variability increased, and there was evidence of increasing vagal and decreasing sympathetic tone. Administration of tolrestat may be of potential benefit in decreasing the likelihood of ventricular arrhythmias and sudden death in diabetic patients with autonomic neuropathy. Yanhu et al. (abstract 1682) treated 32 diabetic patients with the ARI baicalin, which resulted in an 50% decrease in erythrocyte aldose reductase activity with stabilization of nerve conduction and a 58% improvement in neuropathic symptoms vs. a 30% improvement in a control group. Finally, Cross et al. (abstract 619) and Yamanoto et al. (abstract 628) reported polymorphism of the aldose reductase gene to be associated with susceptibility to nephropathy, further suggesting that research in the use of ARI, perhaps in combination with other agents, may lead to effective treatment of diabetic complications. Based on research of other mediators, Solerte et al. (abstract 658) reported that patients with type 2 diabetes and peripheral neuropathy had increased tumor necrosis factor-α and decreased IGF-1 generation from natural killer cells, which indicates a "neuroimmunoendocrine role of inflammatory cytokines and growth factors in the development of nerve functional disorders."

Ito et al. (abstract 645) reported decreased levels of serum nerve growth factor, which correlated with the degree of sympathetic nerve dysfunction, in patients with diabetes. Vinik (abstract 232) reviewed phase 1 and phase 2 studies of 250 diabetic patients with polyneuropathy who were treated with recombinant human nerve growth factor (rhNGF). Diabetic polyneuropathy targets high-affinity TrkA and low-affinity p75 receptors that are implicated in small nerve fiber function (19). rhNGF caused injection-site hyperalgesia in 94% and myalgia in 16% of the cases, and the cooling detection threshold improved in the rhNGF-treated patients. However, 1,500 and 1,019 patients who were enrolled in two randomized multicenter double-blind placebo-controlled studies showed a lack of overall efficacy of this treatment, although Vinik commented that "there undoubtedly have been patients who have had a remarkable response."

Studies of cardiac and gastrointestinal neuropathy were also presented at the ADA Annual Meeting. Pop-Busui et al. (abstract 233) used postmortem emission tomography and 14C-hydroxyephedrine scanning to study regional changes in left ventricular
Peripheral Neuropathy and Foot Ulcers
Peter Cavanogh, Seattle, WA, reviewed the assessment and treatment of foot ulcers. A suggested terminology categorizes foot wounds as any break in the cutaneous barrier. Neuropathy should be emphasized as the major component of the pathogenesis of foot wounds, and ischemia should be considered a secondary factor. Most foot wounds are chronic, that is, they do not progress to healing. Any foot wound that has not healed in 4 weeks leads to worse outcomes. Of individuals with diabetes, 15% will develop a foot ulcer; 25% of these patients will eventually require an amputation.

The treatment goal is to provide treatment for the patient to reach the stage of complete healing, as defined by reepithelialization. The size of the wound may relate more to the time required for healing than to the severity of the wound per se. Ulcer recurrence, defined as a second episode occurring >30 days after healing, occurs within 2-5 years in at least half of diabetic patients who have developed foot ulcers. Cavanogh commented that "wound care should not be considered complete until a systematic strategy for the prevention of recurrence has been implemented." Moreover, he noted that current health care packages inadequately cover treatment of foot-related problems; Medicare, in particular, covers only one podiatric visit every 61 days and one pair of shoes with three inserts every year per patient.
throw in ischemia, what might be mild becomes a severe infection. "Vascular reconstruction outcomes compare favorably for patients with and without diabetes, with aggressive distal revascularization decreasing the need for amputation. Amputation, however, is sometimes the preferred course of action and can improve the patients' overall health. Hyperbaric oxygen has not been shown to benefit neuropathic foot wounds, although it is still used in occasional centers. Emerging techniques include the use of growth factors, such as recombinant PDGF, which may be of benefit, and electrical stimulation, for which there are insufficient clinical data.

Several clinical studies of peripheral neuropathy and lower-extremity ulceration were presented at the ADA Annual Meeting. Vigliotta et al. (abstract 635) followed 246 patients with type 2 diabetes. More than 80% of those patients with HbA1c concentrations >7.5% had peripheral neuropathy, whereas the incidence of neuropathy among the 35% of patients with HbA1c concentrations <7.5% was 8.5% at 12 months, 16.2% at 24 months, 20.5% at 36 months, 30.2% at 48 months, and 40% at 60 months. These data suggest that either nonglycemic factors play a role in neuropathy or that even better levels of control are required to avoid the development of neuropathy in this population. Stansberry et al. (abstract 395) infused 90 mg of the bisphosphonate pamidronate in five patients with diabetic Charcot neuroarthropathy. Cutaneous blood flow after local warming decreased by one-third, suggesting an anti-inflammatory effect, although sensation was not affected. However, Subramanian et al. (abstract 621) reported no difference in bone-specific alkaline phosphatase, an osteoblastic marker, between 25 type 2 diabetic patients with and without neuropathy. These findings indicate that neuropathy does not cause generalized effects on bone in patients with diabetes. Abbott et al. (abstract 337) studied 6,548 patients, 21% of whom had neuropathy and 20% of whom experienced loss of pedal pulses at baseline. At 2 years, 284 patients had new foot ulcers, and relative risk of developing new foot ulcers was increased 9.5-fold among patients who had a leg amputation by the time of baseline; 4.5 to 5.0-fold among patients who showed insensitivity to 10 g monofilament, decreased vibratory sensations, or absent ankle reflexes at baseline; and 2.9-fold among patients who showed reduced frequency of foot pulses at baseline. These findings suggest that "simple clinical measures of peripheral neuropathy [...] are the best predictors of foot ulceration." Harrington et al. (late-breaking abstract 15) reported that a 5% sample of Medicare claims from 1995 and 1996 showed that 7% of Medicare beneficiaries with diabetes sought treatment for foot ulcers. The average Medicare expenditure was $15,309 for diabetic patients vs. $5,226 for Medicare patients in general. On average, 24% of Medicare expenditures for the treatment of these diabetic patients went to treatment of foot ulcers, of which 74% was for in-patient costs. Annually the total Medicare expenditure for treatment of diabetic patients with foot ulcers in 1995 and 1996 was $1.5 billion. However, of those patients who sought treatment for foot ulcers, 70% had little or no regular follow-up. Amato et al. (abstract 829) followed 183 diabetic patients with foot ulcers for up to 9 months and reported an estimated annual indirect cost of $391 and an annual direct cost of $5,066 per patient. Of the average direct cost, 53% was used to pay for in-patient services. The national annual direct and indirect costs of diabetic foot ulcer care in the U.S. were estimated to be $5 billion and $400 million, respectively. Pfeifer et al. (abstract 235) provided analgesic relief to nine patients who suffered from bilateral lower-extremity refractory diabetic neuropathy by administration of topical clonidine. Negligible systemic absorption was evidenced by the lack of blood pressure changes and the lack of detectable plasma drug concentrations. Walker et al. (abstract 648) reported that 10 patients with neuropathy and diabetic amyotrophy, as compared with 14 patients who had a similar degree of neuropathy alone, had marked weakness and pain in the pelvis and femoral region. A nerve biopsy showed a distal loss of myelinated fibers with axonal atrophy and unmyelinated fiber regeneration, which may, perhaps, contribute to the pain syndrome. Suzuki et al. (abstract 70) measured fat-to-water and phosphocreatine-to-inorganic phosphate ratios with magnetic resonance studies in 36 type 2 diabetic patients who had neuropathic foot ulcers. In these patients, plantar muscle adiposity was increased and high-energy phosphate levels were decreased. Armstrong et al. (abstract 71) reported that percutaneous Achilles tendon lengthening increased ankle dorsiflexion and decreased peak plantar forefoot pressure in 10 diabetic patients who previously had plantar ulcers. These findings suggest that percutaneous Achilles tendon lengthening may play a role in ulcer healing and may reduce the risk of ulcer recurrence. Van Schie et al. (abstract 73) injected 1.2 ml of liquid silicone or an equal volume of placebo (saline) under metatarsal head areas with callus in 28 neuropathic diabetic patients without peripheral vascular disease. At 12 months, reduction in callus formation was reported in 69% of the silicone-treated patients vs. 45% of the placebo-treated patients. At 24 months, plantar tissue thickness increased 0.9 mm in the silicone-treated patients, whereas it decreased 0.8 mm in the placebo-treated patients. Pham et al. (abstract 74) randomized 10 patients with nonischemic and noninfected plantar ulcers to a weekly application of the human skin equivalent Apligraf (Organogenesis, Canton, MA) versus a saline-moistened gauze to 12 patients for a maximal duration of 4 weeks. Proper wound care, including debridement and weight-off-loading, was provided to all of the patients. The Kaplan-Meier median time to complete closure was 42.5 days in the Apligraf-treated patients vs. 91 days in the control patients. Complete wound closure was achieved in eight of the Apligraft-treated patients vs. five of the control patients (P = 0.069). Jude et al. (abstract 75) reported a 57, 30, and 13% prevalence of gram-positive aerobes, gram-negative aerobes, and anaerobes, respectively, in swab cultures of 79 ulcers. Most gram-positive aerobes were Staphylococcus aureus. Of these, 40% were methicillin resistant, particularly in patients with prior antibiotic treatment, and required a median of 35 weeks to heal vs. 18 weeks to heal for non-methicillin resistant gram-positive aerobes. P-selectin binds to a monocyte and neutrophil receptor and thereby stimulates tissue factor synthesis, acting as a prothrombotic factor in the microcirculation of septic tissue. Ferber et al. (abstract 76) reported a 50 vs. 7 and 8% P-selectin expression on platelets in diabetic patients with infected foot ulcers vs. diabetic and nondiabetic control subjects, respectively, which stresses the importance of anti-platelet therapy with early anti-inflammatory treatment of infected foot ulcers. Lipsky et al. (abstract 517) treated 835 patients with diabetic foot ulcer infection who were without extensive cellulitis, osteomyelitis, exposure of bone or tendon,
Erectile Dysfunction

Alan Garber, Houston, TX, discussed erectile dysfunction (ED). Diabetes increases the risk of ED threefold. ED is seen in 39, 48, 57, and 67% of men with diabetes at ages 40, 50, 60, and 70 years. In addition to age, neuropathy, and retinopathy, risk factors include alcohol use, glycemic control, intermittent claudication, cardiac disease, hypertension, cigarette use, and depression. The typical history is of decreased penile rigidity, occurring over a period of months to years, that eventually leads to an inability to sustain an erection. Acute worsening is suggestive of vascular disease or, particularly in younger patients, psychological neuroses. Androgen deficiency is more likely to decrease libido, and hyperprolactinemia and thyroid dysfunction are relatively infrequent causes of a decreased sex drive. Autonomic neuropathy is the major factor resulting in ED. Of men with diabetes, 82% of those with but 10% of those without erectile dysfunction have bladder dysfunction. Somatic neuropathy also is frequently associated with ED in diabetic men. There is evidence of vascular disease in 50–80% of men with ED, however, reflecting abnormalities in major arteries, cavernosal artery insufficiency, and, possibly, microvascular disease. Treatment includes administration of the α-adrenergic receptor antagonist yohimbine, for which there are no randomized clinical trial data showing benefit. Vacuum devices, transurethral and intracavernosal prostaglandins, penile prosthesis, venous leakage, and arterial surgery. Administration of sildenafil, a phosphodiesterase inhibitor, is effective in ~50% of patients with diabetes and ED. The majority of responders to this treatment has shown continued benefit over a 2-year follow-up period. α-Blockers, such as phentolamine, act by decreasing sympathetic tone, and they are effective in ~30% of patients (20). The dopaminergic receptor agonist apomorphine acts centrally, and it appears to be effective in ~25% of patients with diabetes. However, it causes feelings of nausea in 40% and vomiting in 10% of treated patients. An important question that was addressed by Robert F. DeBusk, Palo Alto, CA, is whether a given patient is at risk of coition-induced MI or sudden death. The amount of physical exertion associated with sexual activity is equivalent to walking at a pace of only ~3 miles/h, during which the heart rate is increased above only that for moderate activity for patients with angina. (21) Exercise tolerance testing (ETT) is useful in patients who have been physically inactive, but it proves to be only modestly predictive for sudden death and slightly predictive for acute MI. DeBusk reviewed data showing that 8% of patients with ischemia on ETT vs. 1% of those patients with negative ETT have MI or sudden death during the subsequent 6 years. Most cardiac events actually occur in individuals whose ETT is negative. DeBusk bemoaned the misperception that cardiologists can “not only provide a stamp of approval but a guarantee” that a given individual will be able to safely enjoy sexual activity. Of overall events, only ~1% of acute MI are triggered by sexual activity, “a very infrequent albeit high-profile problem.” The risk of events among users of sildenafil is also low and appears to be more related to underlying CVD than to the drug itself.

Several studies at the ADA Annual Meeting reviewed the assessment and treatment of ED. Blonde et al. (abstract 385) and Hirsch et al. (abstract 388) reported that in a randomized study of 252 men with ED, patients and partners consistently evaluated sildenafil as being associated with more satisfactory intercourse than placebo. After 12 weeks, 112 of 126 patients on active treatment were taking 100-mg doses of sildenafil. Flushing, headache, rhinitis, dyspepsia, and abnormal vision were reported in 10, 6, 5, 3, and 3%, respectively. Takahashi et al. (abstract 1521) surveyed 708 diabetologists in Japan, 75% of whom were men, and 340 men with diabetes in regard to symptoms of patients with diabetes. Patients vs. diabetologists reported a 30 vs. 8.5% prevalence of ED, a 24.7 vs. 9.3% decrease in sexual desire, and a 4.7 vs. 15% prevalence of cardiac disease. In assessing quality of life, diabetologists greatly emphasized blindness and cerebrovascular and cardiac diseases, whereas diabetic patients included also ED as an important factor. Rajbhandari et al. (abstract 1689) reported that the warm temperature discrimination threshold was a better predictor of ED than cardiac autonomic function or ankle-brachial pressure testing in a study of 18 patients with and 25 patients without ED.

References

8. Staessen J, Fagard R, Thijs L, Celis H, Ara-


