Diabetic Neuropathy

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This is the seventh and final in a series of articles on presentations at the American Diabetes Association's 66th Scientific Sessions, Washington, D.C., 9–13 June 2006. This article reviews aspects of diabetic neuropathy and lower-extremity vascular disease.

At a debate between A. Lee Dellon (Baltimore, MD) and Arthur Vinik (Norfolk, VA) on the role of nerve decompression in the management of diabetic peripheral neuropathy, Dellon discussed evidence in favor of this approach, commenting that hand symptoms clearly may respond to decompression surgery, and suggesting that similar phenomena may be more common than usually supposed in the lower extremity. The tarsal tunnel syndrome was described in case reports more than four decades ago (1). Anatomically, there is a medial plantar tunnel, similar to the carpal tunnel, and a lateral tunnel similar to that of the ulnar nerve, both of which are well-recognized as causes of nerve pressure injury. Dellon cited a review authored by Vinik and Boulton that described tarsal tunnel and peroneal nerve entrapment neuropathies (2), as well as a procedure he has devised to address multiple potential lower-extremity nerve compression sites of the tibial and peroneal nerves. Using continuous pressure threshold determination to assess large-fiber distal diffuse sensory polyneuropathies, over 7-year follow-up of 60 persons undergoing the procedure, all those with evidence of localized nerve dysfunction and half of those with diffuse disease improved. He reviewed primate studies in which compression causes progressive loss of nerve myelin, which improves with release of pressure. The double-crush hypothesis suggests that a particularly important cause of peripheral nerve dysfunction is an injury at more than one site (3), with recognition that "an underlying metabolic disease like diabetes may serve as the first crush." In diabetic animal models, the nerve is edematous, with decreased axoplasmic flow, as well as stiffness of nerve as of blood vessels and other tissues, perhaps caused by advanced glycation end products (AGEs). Dellon reviewed his study of streptozotocin (STZ)-induced diabetic rodents with neuropathy, assessed by measurement of walking-path testing abnormality, in which tarsal nerve tunnel removal surgery prevented the development of neuropathic walking patterns (4); a similar study showed both gait and electron microscopic evidence of benefit of the procedure (5). Combination tarsal tunnel and common peroneal nerve simultaneous-release procedures, Dellon noted, show even greater protective benefit. Clinically, 14 studies have been carried out at a variety of centers in the U.S. and internationally, with reports of a total of 833 persons showing low rates of new ulcers and no amputations. He described a study of 50 persons who were operated on one leg only, with a mean 4.5-year follow-up showing 12 new ulcers and three amputations, occurring only on the nonoperated side. These findings led to Dellon's assertion that "we believe we can change the natural history of diabetic neuropathy." Balance and protection against falls, he noted, depend on input from the feet. Assessment of sway with computer force plate measurement shows an increase in persons with diabetic neuropathy with the eyes closed, with normalization of sway and evidence of recovery of sensation occurring after the decompression procedure.

Dellon suggested that Tinel's sign of tingling distal to percussion over the site of an injured nerve is useful in determining persons who will benefit from the decompression procedure. He studied 46 diabetic persons with positive and negative Tinel's sign. Of 40 patients with positive Tinel's sign, 37 improved with surgery, while only two of six with a negative Tinel's sign improved, suggesting this to be an important approach that also allows the physician to identify a site of nerve entrapment. The International Neuropathy Decompression Registry (www.neuropathyregistry.com) gives information pertaining to outcome of 786 operations performed on 583 persons by 37 different surgeons. Of 41 persons who have had previous ulcers, 51 operations have been performed, with ~5% developing new ulcers over 5 years of follow-up.

Arthur Vinik took an opposing position, emphasizing the need to balance the evidence that there may be some persons with entrapment against what he characterized as the rarity of tibial and medial nerve entrapment, the need to distinguish mononeuritis from entrapment, and the need to realize that persons with diabetic neuropathy are very likely to have a placebo effect in response to any intervention. Diabetic neuropathy may well be completely asymptomatic, and painful neuropathy may be becoming less common. Furthermore, it is important to distinguish painful neuropathy from other conditions such as Morton's neuroma (a nontumorous thickening of tissue surrounding a digital nerve, typically under the ligament connecting the third and fourth metatarsals), claudication, and osteoarthritis. There are many different diabetic neuropathies involving many different nerve types, with large-fiber nerve function abnormality causing weakness, wasting, and impaired position sense, whereas small-fiber abnormality more often presents with pain, which may be burning, superficial, hyperesthetic, and hyperalgesic initially (although, subsequently, these sensations lessen), as well as autonomic features and change in perception, often without electrophysio-

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Abbreviations: ABI, ankle-brachial index; AGE, advanced glycation end product; CVD, cardiovascular disease; MRA, magnetic resonance angiography; PAD, peripheral arterial disease; STZ, streptozotocin; VEGF, vascular endothelial growth factor.

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logical abnormality, loss of strength, or abnormal reflexes. In diabetic neuropathy, nerve fibers are lost over time, and Vinik suggested that these are unlikely to regenerate after surgical decompression. He emphasized that improvement in symptoms may actually be related to worsening of neuropathy with loss of sensation, so that it is crucial to prove that a strong biologically relevant response occurs following a major procedure such as that proposed by Dellon, with a low number needed to treat and a high number needed to harm.

The most sensitive measurement for assessment of peripheral neuropathy, Vinik suggested, is the vibration perception threshold (the cooling detection threshold is also sensitive), while current perception and two-point discrimination are less effective, with Vinik emphasizing that "this is the difficulty" in interpretation of Dellon's decompression studies. Furthermore, he emphasized that acute painful mononeuritis will resolve spontaneously and should be distinguished from entrapment, as its treatment comprises rest, splinting, and perhaps diuretics and steroid injections.

Vinik reviewed an analysis of carpal tunnel syndrome in 81 persons in which Phalen's sign (symptoms in the median nerve distribution following extreme wrist flexion for 1 min) and Tinel's sign had >80% sensitivity, but noted that Tinel's sign often is falsely positive, with fibromyalgia and tendonitis potentially producing similar symptoms in response to percussion. "What about the tarsal tunnel syndrome," he asked, wondering, "Does this exist?" He noted that peroneal nerve entrapment is relatively common, but stated that compressive neuropathy occurs infrequently with the tibial nerve, arguing against Dellon's assertion. Furthermore, he reviewed a study of duloxetine administration in which there was a 30% reduction in pain in 50% of placebo patients within 2 weeks, as well as a gabapentin study showing 20% reduction in pain in 50% of placebo patients. He also noted that pain decreases in the diabetic foot with a variety of "mechanical noise"–generating devices, including infrared therapy or transcutaneous electrical nerve stimulator (TENS), suggesting that the apparent benefit of the surgical procedure might have many explanations unrelated to actual benefit. The decompression studies have not demonstrated changes in foot pressures or electrodiagnostics, and Vinik suggested that two-point discrimination is not "robust" in quantification of function. Furthermore, he asked, "Could we possibly do damage?" Thus, without demonstration of a block in nerve conduction, and without use of validated measures to prove benefit, he questioned whether Dellon's approach should be continued.

Neuropathy: clinical characteristics

Elliott et al. (abstract 794) followed 3,250 type 1 diabetic patients in the EURODIAB Prospective Complications Study (abstract numbers refer to the American Diabetes Association Scientific Sessions, *Diabetes* 55 [Suppl. 1], 2006). At baseline mean age was 33 years, mean diabetes duration was 15 years, and mean follow-up was 7 years. A total of 276 patients had neuropathy on standardized evaluation, 134 males, of whom 46 had deep or burning pains in the legs; 126 developed prickling sensations in the feet; and 130 had no pain in the legs or feet; those experiencing pain were half as likely to have micro- or microalbuminuria, and 74% of those with pain as opposed to 48% of those without pain were female. The authors comment that the greater likelihood of normoalbuminuria may reflect earlier neuropathy with less peripheral nerve dysfunction. In additional analysis of this study, these authors (abstract 793) assessed large-fiber dysfunction by biothesiometry, showing reduction in vibration sensation in 24% of the cohort, associated with diabetes duration, A1C, and, after correction for these parameters, with male sex, hypertension, LDL cholesterol, cigarette use, weight, retinopathy, nephropathy, and cardiac autonomic neuropathy. Abnormal vibration perception was associated with greater likelihood of gangrene, amputation, foot ulceration, leg bypass or angioplasty, and mortality. Malik et al. (abstract 797) followed 1,594 diabetic persons, with mean age 64 years and diabetes duration 10 years, for a 10-year period, grading the degree of neuropathy by examination of light touch, pain, reflexes and vibration, and by biothesiometry measurement of vibration perception threshold, the latter correlating with the sensory neurological examination findings, diabetes duration, and blood pressure, but not with A1C, cholesterol, or BMI. Biothesiometry score was associated with risk of ulceration and amputation, as well as of worsening retinopathy and nephropathy.

Tavakoli et al. (abstract 166) quantified small-nerve fiber morphology using corneal confocal microscopy, a 2-min noninvasive in vivo clinical examination technique, in 102 diabetic patients aged 58 with 15-year duration of diabetes, finding strong correlation with other measures of neuropathy severity; in type 1 diabetic persons who had had pancreas transplantation, they found improvement in this measure after 6 months (abstract 812). In a biopsy study of skin from the dorsum of the foot, Quattrini et al. (abstract 161) and Krishnan et al. (abstract 160) measured blood vessel density and vascular endothelial growth factor (VEGF) expression. In 86 persons with diabetes, as compared with 31 control subjects, blood vessel density was normal but epidermal (though not dermal) VEGF expression was reduced, particularly in those with more severe neuropathy, which the authors speculated might contribute to delayed healing of foot ulcers. Comparing 15 control subjects and 10 and 12 diabetic patients with painful and painless neuropathy, respectively, a measure of C-fiber function, axon reflex vasodilation induced by heating the dorsum of the foot skin to 44°C, correlated with VEGF levels and was reduced in both groups with neuropathy, particularly in those with painless neuropathy, further suggesting that the presence of pain implies a lesser degree of actual nerve damage.

Neuropathy treatment

Several studies in animal models suggested potential treatment approaches for diabetic neuropathy. Ota et al. (abstract 802) reported that metformin, which is structurally similar to the anti-glycation agent aminoguanidine, produced dose-dependent reduction in apoptosis induced by the AGE methylglyoxal with evidence of decreased oxidative stress in cultured mouse Schwann cells. Matsumoto et al. (abstract 525) administered the aldose reductase inhibitor ranirestat to STZ-diabetic mice, showing reduced nerve sorbitol to 4% of that in untreated diabetic animals, with preservation of axonal and myelin areas and prevention of loss of nerve conduction velocity and of cataract formation. Logendra et al. (abstract 520) reported that an extract of *Artemisia dracunculus L* (Russian Tarragon) has action as an inhibitor of aldose reductase. Govorko et al. (abstract 478) reported that the extract reduced

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phosphoenolpyruvate carboxykinase, potentially decreasing gluconeogenesis, while Wang et al. (abstract 613) showed reduction in protein tyrosine phosphatase-1B activity in cell culture of muscle cells obtained from type 2 diabetic persons. Kellogg et al. (abstract 806) reported that cyclooxygenase-2 gene inactivation in a STZ-induced diabetes model for 6 months was associated with improved nerve conduction and quantitative sensory testing of large and small myelinated and small unmyelinated nerve fibers. Inoue et al. (abstract 162) administered pioglitazone to STZ-diabetic rats, finding improvement in nerve conduction with upregulation of uncoupling protein-3, increased expression of antioxidative genes, and normalization of mitochondrial DNA in the dorsal root ganglion of treated animals. Kamiya et al. (abstract 165) administered C-peptide for 3 months to a type 1 diabetic rat model, finding restoration in reduction of sural nerve unmyelinated fiber number and mean axonal area with improved nerve growth factor content and expression of the insulin and IGF-1 receptor in dorsal root ganglia, with improved hyperalgesia.

In a clinical study, Kipnes and Ando (abstract 7-LB) administered intramuscularly a formulation of a plasmid DNA expressing an engineered zinc finger DNA-binding protein transcription factor to activate VEGF in 18 persons with diabetic neuropathy. There was no evidence of toxicity, and pain improved in 6 patients, numbness improved in 6 patients, and vibration threshold sensitivity improved in 9 of 12 evaluable patients. Rice et al. (abstract 550) administered topiramate in gradually increasing doses from 25 to 100 mg daily over 6 weeks, with a subsequent 12-week period of treatment at full dose, to 20 diabetic persons with peripheral neuropathy, with evidence of improvement in quality of life in association with enhanced proximal leg cold perception, suggesting that the agent may be more tolerable when titrated in this fashion. In an in vitro study suggesting that the agent may have structural as well as functional benefit, Pittenger et al. (abstract 805) incubated neuronal cells with topiramate, a model in which cell proliferation and anti-apoptotic effects have been shown, finding increased laminin receptor-1, α-4 integrin, hepatic nuclear factor-4, calmodulin-dependent kinase IV, and Δ-chain precursor of the acetylcholine receptor. Hardy et al. (abstract 796) presented a combined analysis of 867 persons with diabetic peripheral neuropathic pain randomized to duloxetine 60 mg twice daily versus placebo for 52 weeks, finding 0.5 vs. 0.2% increase in A1C, and a 12 mg/dl increase vs. a 12 mg/dl decrease in fasting glucose, suggesting that glycemic control should be closely monitored with use of this agent. Kajdasz et al. (abstract 577) reported a dose-related increase in heart rate of 2 bpm with 60 mg and 5 bpm with 120 mg duloxetine daily in 12-week studies of 344 and 341 persons, with 339 persons receiving placebo having a 1-bpm decrease in heart rate during this period. No differences were observed in blood pressure or cardiovascular disease (CVD) events.

Diabetes and the central nervous system

Diabetes may be associated with central as well as peripheral nervous system dysfunction. Li et al. (abstract 810) reported decreased frontal cortical neuronal density in rat models of both type 1 and type 2 diabetes, with increased expression of amyloid precursor protein, concordant with reports that diabetes may be associated with Alzheimer's disease. Saczynski et al. (abstract 243) reported an association of type 2 diabetes with reduced speed of processing and executive cognitive function among persons over age 75 years in an analysis of 2,300 persons in a population-based study in Reykjavik, Iceland. In a subanalysis of this group, Pelia et al. (abstract 958) performed magnetic resonance imaging of 1,977 study participants, finding subcortical and periventricular white matter lesions to be present in excess approximately twice as often in the 12% with type 2 diabetes. Hu et al. (abstract 242) studied a cohort comprising 51,552 Finnish men and women aged 25–74 years followed 18 years, 633 developing Parkinson's disease. Diabetes was associated with a 78% increase in Parkinson's disease, controlling for age, sex, obesity, blood pressure, cigarette, alcohol, coffee, tea use, education, and activity. Interestingly, in a study by Selvarajah et al. (abstract 809) of 23 diabetic persons using proton magnetic resonance spectroscopy of the right postero-lateral thalamic nucleus, those with neuropathy without pain symptoms had reduced thalamic sensory neuronal function, while those without neuropathy and those with painful neuropathy had preserved thalamic neuronal function, which may be required for pain perception. Although falls may reflect peripheral as well as central neurologic dysfunction, it is noteworthy that Schwartz et al. (abstract 963), analyzing data from the Health, Aging and Body Composition study of 3,075 white and black, well-functioning men and women age 70–79 years, found that the 24% with diabetes had 12 versus 7 hospitalizations with fall injuries per 1,000 patient-years. Diabetes increased the risk of such hospitalizations 1.8-fold after adjustment for age, race, sex, cognitive function, vision, weight, history of fainting, benzodiazepine use, antidepressant use, prevalent coronary heart disease, chair stands, gait speed, standing balance, renal function, and falls in the year before baseline.

Lower-extremity vascular disease

Mark A. Creager (Boston, MA) discussed the epidemiology and prognosis of peripheral arterial disease (PAD). PAD can be defined as the presence of a stenosis or occlusion, usually atherosclerotic, in the arteries of the lower abdomen and lower extremities, and is associated with increased risk of coronary and cerebrovascular disease. Based on National Health and Nutrition Examination Survey (NHANES) data, PAD affects ~4% of persons at age 40, with prevalence increasing at older ages, approximating 20% of those age 65–70, and close to one-third of those over age 70 and with risk factors, particularly diabetes and cigarette smoking, as well elevated cholesterol level. Framingham data based on symptoms of claudication showed that PAD was two-to eightfold more likely over 30-year follow-up in persons with diabetes. The combination of PAD and diabetes is associated with markedly increased mortality, as well as with increased risk of amputation. In a study of >6,900 persons over age 70 and of cigarette smokers and persons with diabetes over age 59, 24% had PAD, almost half of whom had no other known manifestations of atherosclerosis, suggesting the importance of this diagnosis. PAD is asymptomatic in approximately half of patients, with only 15% having typical claudication. Approximately one-third have difficulty walking, and 1–2% have critical limb ischemia with rest pain, ulcers, or gangrene. One way to detect PAD is to measure the ankle-brachial index (ABI), the ratio of the systolic blood pressures measured by

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Doppler at the two sites. Both brachial artery blood pressures should be measured, and the ratio of the higher of the two ankle pressures to the higher of the two brachial pressures is the ABI, which should be >0.9. Claudication typically occurs at ABI 0.5–0.9, and critical limb ischemia at ABI <0.5. Creager suggested that the ABI should be determined in all persons with diabetes over age 50 years and in younger persons with diabetes with risk factors, recognizing that vascular calcification may make the measurement inaccurate. Additional vascular studies include segmental pressure measurements, an extension of the ABI to assess pressures at more proximal sites, pulse volume recordings, giving an index of the rate and degree of rise, and imaging studies including magnetic resonance (MR) and computerized tomography (CT) angiography, the former not requiring radiation or iodinated contrast, the latter offering somewhat better resolution although requiring radiation exposure and exposing the patient to iodinated contrast.

PAD is associated with a sixfold increased risk of CVD mortality, with a falling ABI associated with a particular increase in mortality, although high ABI (typically secondary to vascular calcification) is also associated with increased mortality. Progression of PAD occurs in 20–25% over a 5-year period, with critical limb ischemia a particularly severe outcome, associated with 20% mortality and 30% amputation at 6 months. The goals of treatment, then, are to reduce the risk of adverse cardiovascular events and to improve limb outcome. Strategies include lifestyle modification, including activity and diet, smoking cessation, glycemic control, aggressive dyslipidemia and blood pressure treatment, and use of antiplatelet therapy. In the Heart Protection Study, persons with atherosclerosis and with diabetes plus additional risk factors randomized to simvastatin had 24% decreased risk of myocardial infarction or death, and studies with atorvastatin show improved walking distance. Ramipril treatment in the Heart Outcomes and Prevention Evaluation (HOPE) Study led to a 22% decreased risk of cardiovascular events in persons with PAD. A meta-analysis by the Antithrombotic Trialists' Collaboration of 287 studies involving 135,000 patients in comparisons of antiplatelet therapy versus control and 77,000 in comparisons of different antiplatelet regimens included ~9,000 persons with PAD, showing an aggregate 22% decrease in the risk of CVD events (6). The clopidogrel versus aspirin in patients at risk of ischemic events (CAPRI) trial compared aspirin with clopidogrel in people with evidence of atherosclerosis, showing an 8.7% decrease in risk of myocardial infarction, ischemic stroke, or death with clopidogrel; people with PAD had 24% fewer CVD events with this agent (7). The CHARISMA trial of persons with atherosclerosis or increased risk thereof (including diabetes, albuminuria, hypertension, hypercholesterolemia) randomized to aspirin versus aspirin plus clopidogrel showed no overall benefit of the combination, but persons with symptomatic atherosclerosis had a 12% risk reduction with dual treatment, while those with risk factors without documented CVD had a 20% increase in risk (8). Walking programs have been shown to increase walking distance from ~1 to 2–3 blocks, an effective and safe approach. The type 3 phosphodiesterase inhibitor cilostazol and the xanthine derivative pentoxifylline are approved for pharmacological treatment of claudication, with the former more reproducibly associated with improvement in walking distance. Revascularization procedures for rest pain and critical limb ischemia include catheter-based angioplasty procedures, which are effective for aortoiliac disease with 70% 5-year patency rates, although somewhat less effective for femoral disease, while surgery is highly effective but is associated with 1–3% mortality, given the underlying CVD of these patients.

Frank B. Pomposelli (Boston, MA) discussed the short- and long-term outcomes of distal bypass surgery, emphasizing the importance of lower-extremity vascular disease as members of our society age, as well as in persons with diabetes and in cigarette smokers. Amputation should currently, he suggested, be performed in only 10–20% of persons with critical limb ischemia, with bypass allowing limb salvage in the remaining 80–90%, with perioperative mortality rates <2%. Atherosclerosis occurs particularly in the tibial and peroneal arteries, with the pedal arteries, particularly dorsalis pedis, typically spared in persons with diabetes, allowing the surgical treatment strategy of distal bypass. Ischemia often occurs in diabetic persons also having neuropathy and infection, so that all these abnormalities need be addressed. Although agreeing that ABI is a useful screening tool, Pomposelli suggested that simple palpation of the feet should not be underestimated, and that it is important to evaluate all persons without palpable pulses. Persons with neuropathic ulcers require evaluation for ischemia to assure that an adequate vascular supply is present for wound healing, and those found to have PAD typically require bypass surgery early in the course of the illness. Ischemic rest pain occurs particularly in the toes and dorsum of the foot, but may occasionally affect the pretibial area, and may be more pronounced when the patient is supine and relieved by upright posture, features similar to complaints sometimes associated with peripheral neuropathy.

In his series of >1,000 diabetic persons, nonhealing ischemic or neuropathic ulcers are the most common indication for surgery. Adequate venous conduit is important, as grafts tend not to allow successful restoration of circulation. Pomposelli commented that "age alone is not a contraindication" and that it has become "commonplace" to operate on persons over age 80. Ambulatory status and whether the patient lived at home before surgery are important indicators of the potential for positive outcome of surgery. He noted, however, that "mortality is also terrible in patients with major limb amputation," with 5.7% and 16.5% 1-year mortality for persons undergoing below-knee and above-knee amputations. Containdications to bypass are unstable CVD, acute renal failure, particularly after contrast arteriography, end-stage malignancy, and an unsalvageable limb, while inadequate venous conduit and severe venous disease require a catheter-based intervention, so that the likelihood of good recovery is reduced. He recommended that bypass surgery not be performed in the setting of active infection, although one need not delay until all cultures are negative, and return of glycemic control is often an indicator of stabilization of an infection.

Popliteal or distal tibial artery to pedal artery bypass using the saphenous vein gives the best result, with the reverse vein technique often technically inadequate, so that leaving the spahenous vein intact in its bed and sectioning its valves appears the most effective approach, with short segment vein grafts often useful. In 40% of people, the saphenous vein is not available, and the lesser saphenous vein in the calf or an upper-extremity arm vein can be used. He recommended that the contralateral saphenous vein not be used because the frequency of ischemic com-

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plications in the opposite limb is so high, so that patients typically will subsequently require a contralateral bypass procedure. Vein grafts fail because of neointimal hyperplasia, leading to focal areas of narrowing and occlusion, so that close follow-up is essential. Distal bypass is not without difficulty, with 50% of patients requiring re-operation at 3 months, while half of foot wounds will not have healed by this time. One must realize that the course of recovery is long, that less than one-fifth of patients achieve full ambulatory status, and that survival ranges from poor to extremely poor in these persons with multiple risk factors.

Two studies presented at the ADA meeting discussed aspects of PAD in persons with diabetes. Jinnouchi and Jinnouchi (abstract 102) measured the ABI and performed arterial plethysmography in 2,491 persons with type 2 diabetes, finding 206 persons with suspect lower-extremity atherosclerosis who underwent magnetic resonance angiography (MRA). Of this group, most of those with ABI <0.9 had severe arteriosclerosis, with the authors concluding that an optimal cutoff for ABI to include persons with moderate and mild arteriosclerosis is 1.0. This approach, however, does not allow one to determine the frequency of false positives that would be found with this cutoff had MRA been done in all 2,491 diabetic patients. Gregg et al. (abstract 902) used NHANES 1999–2002 data to estimate the age-sex adjusted U.S. prevalences of PAD (ABI < 0.9) and peripheral neuropathy (lacking foot monofilament sensation at at least one of six sites) in persons with normal glucose, fasting glucose 100–125 mg/dl, undiagnosed diabetes (fasting glucose ≥126), and diagnosed diabetes. Neuropathy was present in 10, 12, 17, and 15%, and arterial insufficiency was present in 4, 6, 6, and 9% of the respective groups.

Lower-extremity ulcers

Lower-extremity ulcers remain an important complication of diabetes. Miller and Huang (abstract 246), noting that diabetes is twice as prevalent along the U.S.-Mexico border as nationwide, compared diabetes-related amputation in the 32 Texas counties within 100 km of the border versus the remainder of the state, finding age-adjusted rates of 6.1 vs. 3.7 per 1,000 persons with diabetes, with hospital costs for these procedures correspondingly twice as great as those outside this area. Davis et al. (abstract 892) used government registers of all deaths and hospitalizations in Western Australia to study risk factors for amputation, finding an overall rate of 3.8 per 1,000 diabetes-patient years. A1C, urinary albumin/creatinine ratio, and the presence of peripheral neuropathy, foot ulcer, ABI ≤0.9, retinopathy, and prior cerebrovascular disease increased this risk, with leg amputation in turn a risk factor for cardiac mortality. Miller and Fincke (abstract 946), using a Veterans Administration database, and Abbas et al. (abstract 104), analyzing 252 persons hospitalized in Dar es Salaam, Tanzania, with foot ulcers, both described advantages to foot infection severity classification systems based on distinguishing cellulitis from osteomyelitis, while Jeffcoate et al. (abstract 1,033), in a U.K. population, reported the strongest predictors of ulcer healing, total amputations, and mortality being ulcer area and the presence of ischemia. Izumi et al. (abstract 1,031) followed lower-extremity amputations in 277 diabetic persons over a 10-year period, finding mortality 1.6-fold greater with above-foot than with ray amputation and 2.2-fold higher in those with versus without PAD.

Wound healing

The mechanism of poor wound healing in diabetes is not fully understood. Evans et al. (abstract 101) induced skin blisters on the forearm with cantharidin in 16 type 2 diabetic vs. 30 nondiabetic persons, finding that tumor necrosis factor (TNF)-α levels were 771 vs. 200 pg/ml at 16 h but 378 vs. 806 pg/ml at 40 h. Transforming growth factor-β was undetectable in both groups at 16 h and was 10 ng/ml versus nil at 40 h, suggesting a reversal of the balance of regulatory cytokines in diabetes potentially contributing to abnormality in the control of inflammatory wound healing, with the authors speculating that anti-TNF therapy may be a treatment option in the diabetic foot. In a therapeutic study, Driver et al. (abstract 105) described use of a platelet-rich plasma gel (AutoloGel System; Cytomedix, Rockville, MD) extracted from the patient's own centrifuged plasma in 72 persons with nonhealing diabetic foot ulcers, showing a doubling in the likelihood of healing over that in a control group. Armstrong et al. (abstract 100) compared the outcome of 1,100 persons treated for diabetic foot ulcer with negative pressure wound therapy using the vacuum assisted closure device (KCI, San Antonio, TX) with that of 586 persons treated with wet-to-moist dressings from pooled comparative literature data, finding successful wound healing in 40 vs. 24% at 12 weeks and in 46 vs. 33% at 20 weeks, with expected costs of $16,733 vs. $28,691, suggesting that this may be an appropriate therapeutic approach in the outpatient setting. Such analysis, though involving large numbers, may be questioned as not involving an appropriate control group. Armstrong and Lavery (abstract 1,034) also reported a 16-week randomized clinical trial of the two treatment approaches in 122 acute and 40 chronic large (mean 20.7 cm^2) wounds after partial foot amputation in persons with diabetes treated with negative pressure wound therapy versus moist wound therapy using alginates, hydrocolloids, foams, or hydrogels, finding more rapid healing both in the acute and chronic setting with the former approach. Mancini et al. (abstract 103) treated 20 persons with acute Charcot neuroarthropathy with alendronate 70 mg weekly versus placebo. In the treated group, serum collagen COOH-terminal telopeptide of type 1 collagen decreased 46%, and urinary hydroxyproline 28%, suggesting reduction in bone turnover, with a 33% increase in foot bone density on dual energy X-ray absorptiometry, while these measures did not change in the placebo group.

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