women with IGT but not among men. Reasons may include a large difference in baseline smoking rates between men and women.

Apart from diabetes, measures of risk factors for death (and CV disease) at baseline and during the trial were limited. In turn, the investigators were unable to identify or exclude possible confounding factors for the differences in outcomes between women and men. The reasons remain unclear.

Participants in the intervention group were, on average, 2 years younger than those in the control group, but there were no differences in baseline body mass index (BMI) in controls, 26.2±0.2 kg/m^2 versus BMI in the combined intervention group, 25.7±0.2 kg/m^2. The changes in body weight during the active-intervention period (1986 to 1992) and the entire follow-up period (1986 to 2006) did not differ significantly by group [Guangwei L et al. *Lancet* 2008].

Markers of Macrovascular Complications in Pediatric Diabetes

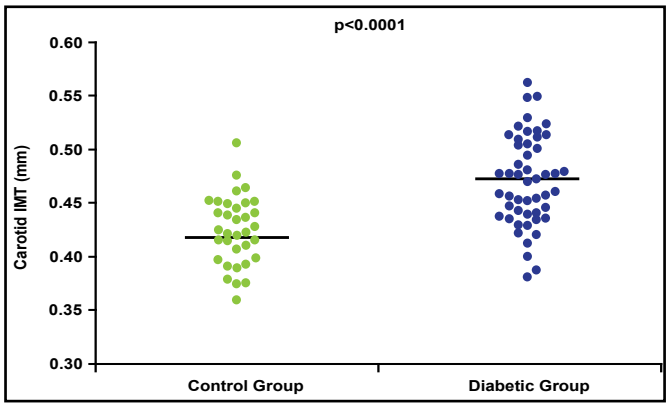
Written by Phil Vinall

Children with diabetes are at high risk for premature cardiovascular disease (CVD), which can lead to mortality later in life. Screening and treatment of modifiable risk factors in young patients with diabetes are important to decrease lifetime risk for CVD. R. Paul Wadwa, MD, University of Colorado School of Medicine, Aurora, Colorado, USA, discussed several noninvasive surrogate measures that would allow for the stratification of CVD risk, and he presented evidence for more aggressive treatment of patients at the highest risk for macrovascular disease in adulthood.

Endothelial dysfunction is considered an early stage in the pathogenesis of atherosclerosis. Evidence indicates that endothelial dysfunction in children with diabetes may predispose them to the development of early atherosclerosis [Järvisalo MJ et al. *Circulation* 2004]. The brachial ultrasound technique can be beneficial for detecting impaired flow-mediated dilation. Another tool for measuring endothelial dysfunction is peripheral arterial tonometry. In one study, children with type 1 diabetes had endothelial dysfunction, as evidenced by lower mean reactive hyperemia peripheral artery tonometry scores when compared with children without diabetes [Haller M et al. *Pediatr Diabetes* 2007].

Noninvasive B-mode ultrasonographic measurement of progression of intima-media thickness in the distal common carotid artery is a useful surrogate endpoint for clinical coronary events. Increases in the thickness of the intima and media of the carotid artery are directly associated with an increased risk of myocardial infarction and stroke in older adults without a history of CVD [O'Leary DH et al. *N Engl J Med* 1999]. Although data are limited in younger patients, one study has shown an increase in carotid intima-media thickness (cIMT) and a decrease in flow-mediated dilation in children (mean age 11 years) with type 1 diabetes (Figure 1) [Järvisalo MJ et al. *Circulation* 2004]. Preliminary data presented at the 2011 meeting of the American Diabetes Association indicate significantly thicker cIMT in the common and internal carotid in youth with type 1 diabetes compared with controls [Urbina EM et al. *Diabetes* 2011].

Figure 1. cIMT in Controls and Type 1 Diabetes.



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In an ancillary study to the SEARCH for Diabetes in Youth study, the measurement of arterial stiffness by pulse-wave velocity, pulse-wave analysis, and brachial artery distensibility indicated that youths with type 2 diabetes had worse arterial stiffness than youths with type 1 diabetes [Wadwa RP et al. *Diabetes Care* 2010]. Further, pulse-wave velocity was higher than controls in youths with type 1 diabetes with a mean age of 19 years but not in youths with a mean age of 15 years, suggesting that the right time for aggressive intervention to prevent vascular damage would be between the ages of 15 to 19 years [Wadwa RP et al. *Diabetes* 2011 (two ADA abstracts)].

Coronary artery calcification correlates with overall coronary plaque burden and can be predictive of future coronary events. Although data in adults with diabetes are strong, coronary artery calcification may be of lesser interest in pediatric patients, as there is a relatively low presence of coronary artery calcification in patients aged <30 years [Starkman HS. *Diabetes Care* 2003].

Echocardiography has been used to document cardiac dysfunction in adults with diabetes. Recent studies have shown that it can detect diastolic dysfunction, increased ventricular septal thickness, and lower circumferential strain compared with nondiabetic controls [Nadeau K

et al. *J Clin Endocrinol Metab* 2010; Salem et al. *Pediatr Diabetes* 2009]. Further work is needed to evaluate risk factors associated with changes in cardiac structure and function.

Most of these techniques are affordable, available, and safe. Currently, however, they are used in clinical research only. Further work is needed to standardize techniques and the development of normative data that account for changes with age and pubertal development. The results need to be reproducible, and their use should be cost-effective and lead to effective treatment/interventions.

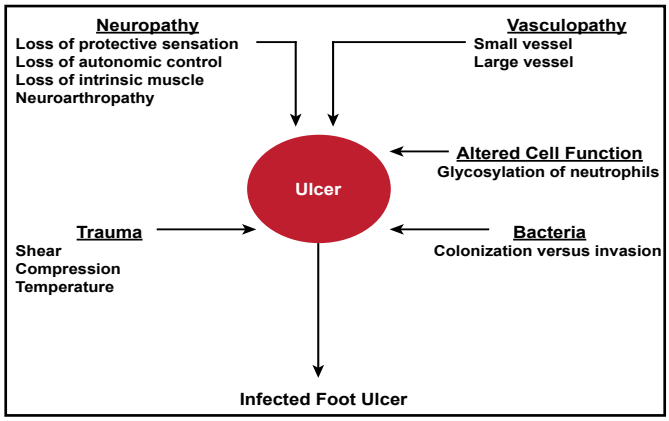
Nonoperative Management of the Infected Diabetic Foot

Written by Rita Buckley

Diabetes affects 25.8 million people of all ages, or 8.3% of the US population. In 2007, it was the seventh leading cause of death. More than 60% of nontraumatic lower limb amputations occur in people with diabetes. In 2006, that number totaled approximately 65,700 [National Diabetes Information Clearinghouse (NDIC) *National Diabetes Fact Sheet* 2011]. During an interactive case-based session, John M. Embil, MD, University of Manitoba, Winnipeg, Manitoba, Canada, discussed nonoperative management of the infected diabetic foot.

Skin serves many functions. It not only affects sensation and appearance, it also maintains fluid and electrolyte balance, protects the body from microbial invasion, and regulates body temperature. Foot ulcer pathogenesis disrupts these functions (Figure 1). When confronted with an infected diabetic foot, physicians must decide on diagnostic and management approaches, including choice of antibiotic and adjunctive measures.

Figure 1. Foot Ulcer Pathogenesis.



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Diabetic foot infections typically manifest with fever, chills, heat, redness, pus, and pain. Wounds can be colonized but not infected or infected. To manage the wound and infection, physicians must address the underlying cause (eg, neuropathy, unrelieved pressure, repetitive injury, underlying infection, foreign bodies, suboptimal circulation, social factors, and footwear). Dressings and other topical therapies are adjuncts to treatment of the underlying cause.

A thorough wound evaluation that includes a history, physical examination, and investigations should guide clinical decision-making (Figure 2). Empiric antimicrobial choices should be broad but based on available microbiology results. The route and duration of therapy will vary, depending on the severity of the infection and the tissues that are involved. Surgical and nonsurgical management of the diabetic foot may be intimately related.

Figure 2. Wound Evaluation.

- History
- Physical Exam
  - Inspection:
    - Location
    - Size
    - Depth
      - Probe to bone
    - Status
      - Erythema, necrosis
    - Odor
    - Exudate
  - Palpation
    - Fluctuance
    - Heat
    - Tenderness
- Investigations
  - Microbiologic
    - Gram stain
    - Culture
      - Bone
      - Superficial
  - Radiographic
    - Plain radiograph
    - Ultrasound
    - Nuclear imaging
    - Computed tomography
    - Magnetic resonance imaging
  - Others
    - Blood counts
    - ESR
    - CRP

Therapies for the infected diabetic foot can include oral, parenteral, and topical antibiotics; adjunctive measures; and bed rest with foot elevation. A trial of culture-directed oral antimicrobial therapy may be considered if: 1) the patient and the osteomyelitic lesion are stable; 2) the magnitude of skin, soft tissue, and/or bone involvement is not extensive; 3) therapy can be tolerated; and 4) clinical improvement is ongoing. The alternative is parenteral antibiotics.

The efficacy of adjunctive therapies remains an area of active research efforts. Randomized controlled studies of silver-based or silver-containing topical antimicrobial agents or dressings for treating uncomplicated leg ulcers, acute wounds [*Drug Ther Bull* 2010], diabetic foot ulcers, or infected or contaminated chronic wounds are sparse, with insufficient evidence for their use in these applications.

Although there is some indication that negative pressure wound therapy may improve healing, clinical evidence is insufficient to prove additional benefit over conventional wound treatment [Gregor S et al. *Arch Surg* 2008]. Ubbink et al. [*Cochrane Database Syst Rev* 2008] also found no valid or reliable evidence that topical negative pressure increases chronic wound healing.