

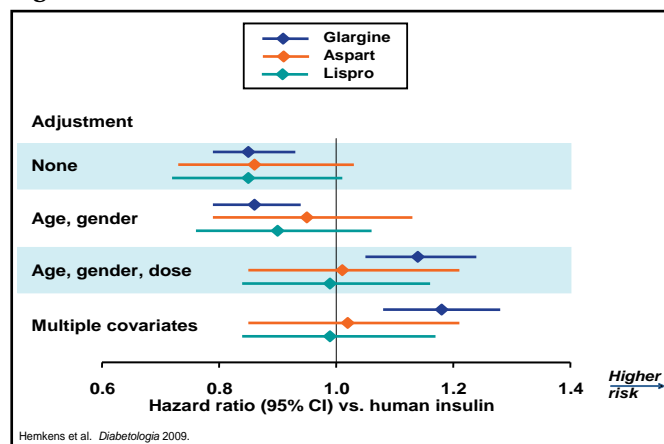
link. In a large cohort of women from New York City, the biological activity of elevated insulin-like growth factor-I levels was demonstrated to have only a modest negative impact on the incidence of colorectal cancer (Ma J et al. *JNCI* 2004).

Could Treatment Play a Role?

Turning to the recent controversy surrounding the use of insulin glargine as a driver of increased cancer incidence, Jay S. Skyler, MD, MACP, University of Miami, Miller School of Medicine, Miami, FL, explained the origin of and media reaction to the proposed theory that insulin glargine may be a carcinogen.

The controversy began in 2009 with an analysis of a German database that suggested that patients who were using higher doses of insulin glargine had an increased risk for cancers of all types but only when adjusted for dose (Figure 2).

Figure 2. Hazard Ratios for Risk of All Forms of Cancer.



This conclusion resulted in several high-profile news articles [Hemkens et al. *Diabetologia* 2009]. This finding prompted the *Diabetologia* editors to request a confirmatory analysis based on unrelated datasets from the United Kingdom, Scotland, and Sweden. The resultant submissions from these public health databases were in general agreement that the association between insulin glargine and cancer was unfounded.

As concluded by Dr. Skyler, "The press headline 'Glargine causes cancer' is unsubstantiated, unwarranted, and unproven."

For additional details and the ADA consensus statement regarding the controversy, see Giovannucci E et al. *Diabetes Care* 2010;33:1674-1685.

The Diabetic Foot Wound

David G. Armstrong, DPM, MD, PhD, University of Arizona College of Medicine, Tucson, AZ, presented the 2010 Roger Pecoraro Lecture at the American Diabetes Association 70th Annual Scientific Sessions, where he discussed management strategies for the treatment of the diabetic foot wound. Every 30 seconds, a lower limb is lost due to complications of diabetes [www.diabeticfootonline.com]. According to the Nord-Trondelag Health Study, foot ulcer history is associated with a 38% increased risk of death among diabetics after adjusting for lifestyle and demographic factors [Iverson MM et al. *Scandinavian J Public Health* 2008].

Dr. Armstrong recommends the team approach to diabetic foot wound management in order to reduce the incidence of amputation. In a study that evaluated 1708 procedures over a period of 32 months, patients who received the team approach to treatment were 61.0% less likely to undergo amputation versus 28.9% in the control group (p<0.0001) [Armstrong DG et al. ADA 2010]. An effective amputation prevention team should include the ability to perform certain tasks, such as site-appropriate culture techniques, vascular assessment and revascularization, neurological evaluation, wound assessment and infection staging/grading, site-specific bedside and intraoperative incision and debridement, culture- and patient-appropriate antibiotic therapy implementation, and postoperative monitoring with a focus on reulceration and infection risk reduction [Fitzgerald et al. *EPlasty* 2009; Armstrong DG et al. *JVS* 2010].

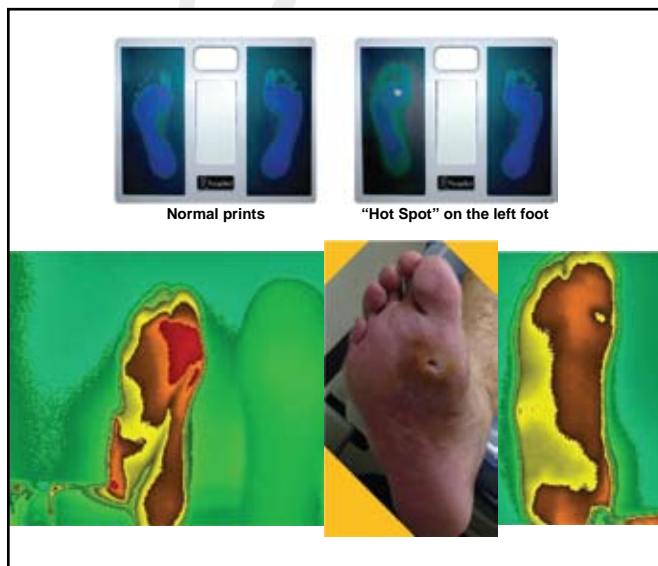
There are also many advances being made in the area of wound care that may optimize the management of diabetic foot ulcers. Among them is vacuum-assisted closure (VAC) therapy. This therapy provides several healing advantages, such as promotion of flap and graft survival, removal of interstitial fluid and infectious material, and uniform wound closure through the use of negative pressure [Saxena et al. *Plast Reconstr Surg* 2004]. VAC therapy resulted in fewer surgical procedures and dressing changes compared with standard moist wound therapy (p<0.0001 for both) [Apelqvist J et al. *Am J Surg* 2008].

Receptor activator of nuclear factor kappa B ligand (RANK-L), osteoprotegerin (OPG), and intranasal calcitonin may also facilitate healing in diabetic foot ulcers. RANK-L and OPG play a key role in bone remodeling and resorption. Dysregulation of RANK-L or OPG may result in bone loss. Upregulation of RANK-L may occur in the

presence of peripheral neuropathies. Intranasal calcitonin may reduce bone turnover, a product of the RANK-L/OPG system, by inhibiting RANK-L. Unlike bisphosphonates, intranasal calcitonin may be used in patients with renal insufficiency [Bern et al. *Diabetes Care* 2004; Bern et al. *Diabetologia* 2006].

Preventing a recurrence remains a priority in diabetic foot ulcer management. Cumulative risk for ulceration by foot risk category may be one way of predicting recurrence. The risk groups range from 0 to 3 based on history and the presence of neuropathy or peripheral vascular disease (0=no neuropathy, no PVD; 1=neuropathy+/- deformity; 2=PVD +/- neuropathy; 3=history of pathology). Skin temperatures may provide important predictive data and indicate impending ulcerations. High temperature gradients between feet may predict the onset of neuropathic ulceration, and regular monitoring of bilateral foot temperatures may allow for early intervention and prevention (Figure 1) [Armstrong DG et al. *Phys Ther* 1997; Armstrong DG et al. *Am J Med* 2008; Lavery et al. *Diabetes Care* 2008]. Monitoring physical activity during drug therapy in the diabetic foot may also be a useful tool in predicting disease progression.

Figure 1. Are Skin Temperatures Predictive of Ulceration?



Reproduced with permission from D. Armstrong, MD.

Optimal diabetic foot management incorporates innovative strategies, such as a team approach, new technologies, and predictive risk assessment tools. Treating the acute foot wound is a complex endeavor, and preventing recurrence is an important part of successful management.

HEALTHY Study Group Achieves Modest Improvement in School-Based Intervention

The HEALTHY study, a name that was selected by the targeted middle school student population, was initiated after a pilot investigation in 2003 documented a high prevalence of risk factors for diabetes in 8th grade students in the United States [*Diabetes Care* 2006]. Indeed, of the 1740 subjects who were observed, 49% had a body mass index (BMI) \geq the 85th percentile (the cutoff for overweightness and obesity); 40.5% had fasting blood glucose (FBG) \geq 100 mg/dl; and 36.2% had fasting insulin \geq 30 μ U/ml, suggesting that middle schools could be logical venues for population-based efforts to prevent or delay the onset of type 2 diabetes mellitus (T2DM).

As described by Kathryn Hirst, PhD, George Washington University Biostatistics Center, Rockville, MD, the HEALTHY study enrolled 6th grade students from 42 middle schools and followed them through 8th grade (n=4603). School eligibility required a \geq 50% minority student body and/or \geq 50% of students who were eligible for free/reduced rate lunch. Schools were randomized 1:1 to either control (observation only) or a comprehensive intervention program that was conducted by teachers and school officials that targeted nutrition, physical activity, and personal behavior [The HEALTHY Study Group. *Internatl J Obesity* 2009].

At baseline, subjects were assessed for physical measurements and fasting blood was drawn to determine FBG, insulin, HbA1C, and lipids; self-reports of diet, exercise, and quality of life were also collected. The same data were collected at the end of study following two and a half years of HEALTHY intervention delivery. Primary endpoints for the study included measures of adiposity, glucose, and insulin.

Gary D. Foster, PhD, Temple University, Philadelphia, PA, reported the primary results of the study [The HEALTHY Study Group. *N Engl J Med* 2010]. For BMI \geq 85th percentile (defined as overweight and obese categories), the changes that were observed for the intervention versus control group were not statistically significant, though significance was seen for BMI z-scores (p=0.04; Table 1). Average waist circumference and FBG were not significantly different; however, significant differences were observed for fasting insulin levels (p=0.04) as well as for reductions in measures