



Dear Federal Working Group on Bone Diseases Members and Diabetes Mellitus Interagency Coordinating Committee,

The summary for the FWGBD and DMICC meeting is below from Dr. Jonelle Drugan, NIAMS. Slides in PDF form are available upon request from Theresa Smith (smiththe@mail.nih.gov).

Please save the dates for the next two **Federal Working Group on Bone Diseases (FWGBD)** meetings will be **Wednesday, July 23, 9:00 a.m. to 11:00 a.m. (EST)** and **Wednesday, November 5, 9:00 a.m. to 11:00 a.m.** at the **National Institutes of Health in Building 31, wing C, 6th floor, room 6**. Please email Theresa Smith with any agenda topics for discussion.

The Federal Working Group on Bone Diseases (FWGBD) and

The Diabetes Mellitus Interagency Coordinating Committee (DMICC)

Combined Meeting on Diabetes and Bone Diseases

February 4, 2014

DIABETES AND BONE: GAPS IN KNOWLEDGE

Ann V. Schwartz, PhD, MPH, Associate Adjunct Professor, Division of Preventive Medicine and Public Health, Department of Epidemiology and Biostatistics, University of California, San Francisco School of Medicine

Dr. Schwarz described some of the data and research gaps related to bone quality in people who have type 1 or type 2 diabetes.

Type 1 diabetes

People who have type 1 diabetes have only somewhat lower than normal bone mineral density (BMD) in the spine and hip ([Vestergaard 2007](#)), but are at markedly increased risk of hip fracture compared with people who do not have diabetes ([Janghorbani et al. 2007](#)). Researchers have yet to demonstrate the mechanisms by which type 1 diabetes leads to reduced bone mass, nor do they understand why the hip

bones of people who have type 1 diabetes are more fragile than dual-energy x-ray absorptiometry (DXA) measures of BMD predict. Data regarding fracture risk at sites other than the hip are lacking.

In response to a question, Dr. Schwartz noted that findings regarding bone accrual in children who have type 1 diabetes were mixed. Studies using tools other than, or in addition to, DXA may be more informative than those using DXA alone.

Type 2 diabetes

Because adults who have type 2 diabetes generally have higher than normal BMD ([Vestergaard 2007](#)), one would expect that they would be protected from fractures. Numerous studies have documented an increased bone fragility in this group of patients, leading to the conclusion that standard approaches for quantifying bone health (i.e., BMD T-scores, the FRAX[®] algorithm) underestimate their fracture risk ([Bonds et al. 2006](#), [Janghorbani. et al 2007](#), [Schwarz et al. 2011](#), [Giangregorio et al. 2012](#)). A noninvasive strategy to identify people who have type 2 diabetes and are at high risk of fracture despite having favorable (or slightly reduced) T-scores remains a worthy goal.

In response to a question about the influence falls have on fracture risk, Dr. Schwartz stated that the higher than average tendency of people who have type 2 diabetes to fall does not fully explain the increased fracture incidence.

The scientific community continues to explore factors that may contribute to the elevated fracture risk of people who have type 2 diabetes. Animal work and two small studies of bone biopsies taken from patients suggest that type 2 diabetes might impair bone formation ([Krakauer et al. 1995](#), [Manavalan et al. 2012](#)). The contributions of hyperglycemia, extreme fluctuations in glucose levels, or insulin resistance to this phenomenon are unclear.

Advanced imaging tools such as quantitative computed tomography (QCT) and peripheral quantitative computed tomography (pQCT) have revealed that type 2 diabetes is associated with microscopic changes in bone structure and marrow composition. A minimally invasive technique called microindentation, which is performed on the tibia under local anesthesia, revealed that women who have type 2 diabetes have compromised bone strength ([Farr et al. 2013](#)). While the reasons for the impaired bone properties associated with type 2 diabetes are unclear, some people hypothesize that the accumulation of advanced glycation endproducts (AGEs) in bone is a contributing factor. Drs. Jepsen and Schlecht commented on the Farr article in the Journal of Bone and Mineral Research (see [“Biomechanical Mechanisms: Resolving the Apparent Conundrum of Why Individuals with Type II Diabetes Show Increased Fracture Incidence Despite Having Normal BMD”](#))

Medications prescribed to treat type 2 diabetes also may influence bone health. Rosiglitazone is associated with a 2-fold increase in fracture risk in women, but not men ([Kahn et al. 2008](#)). The effects of diabetes medications that are not members of the thiazolidinedione family are less well documented, although metformin and sulfonylurea appear to have no influence on fracture risk. The Intensive Glycemic Control and Skeletal Health (ACCORD-BONE) study showed that the fracture rates of participants whose glucose levels were extremely well-controlled were similar to those whose diabetes was managed according to the generally accepted medical standards ([Schwartz et al. 2012](#)). It is worth noting that all ACCORD-BONE study participants maintained good control of their blood sugar levels; the consequences of poor glycemic control on bone health cannot be extrapolated from these findings.

Until additional data specific to bone health in people with type 2 diabetes are available, standard osteoporosis treatment guidelines seem appropriate ([Vestergaard et al. 2011](#)). Dr. Schwartz noted that the reduced bone formation rates seen in this patient population raise a theoretical concern regarding the safety and efficacy of anti-resorptive therapies such as bisphosphonates. There is no clinical evidence that further suppression of turnover may have a negative effect on bone strength, but the studies are limited. In response to a question about whether people with type 2 diabetes should avoid bisphosphonates, Dr. Schwartz speculated that anabolic therapies may be more effective than drugs that reduce bone resorption, but emphasized that there are no data on this.

Discussion

In addition to the questions mentioned above, the following issues were raised during the discussion period.

- Dr. Schwartz noted an association between the time since disease onset and fracture rate, describing this and other associations as fertile ground for research. For example, people who have prediabetes seem to have a reduced fracture risk, even compared with non-diabetic people. The relation between insulin resistance and bone, and the changes that occur in bone when a person transitions from a pre-diabetic to fully diabetic state, remain unclear.
- Vascular supply was mentioned as another variable in type 2 diabetes that might influence fracture risk.
- Information about the roles of neuropathy and kidney function in fracture risk come from two large observational studies of osteoporosis (SOF and MrOS).

METABOLISM AND INTER-ORGAN CROSS-TALK

Clifford J. Rosen, M.D., Director of the Center for Clinical & Translational Research, Maine Medical Center Research Institute

Integration of skeletal tissue with activities of organ systems

After briefly describing the different types of bone cells and a few key signaling molecules that regulate bone formation and breakdown, Dr. Rosen explained how bone cells are connected to other organs and organ systems.

Bone cells originate from precursor cells that also can form other tissues. The osteoclasts, which are responsible for bone resorption, are derived from hematopoietic precursors. Bone-building osteoblasts are derived from the mesenchymal lineage, which also produces cartilage and fat. The differentiation of cells into osteoblasts and adipocytes is closely related; both types of cells share some steps during their development. Terminal differentiation is regulated by transcription factors that are specific to bone or fat.

In addition to a shared origin, osteoblasts and adipose cells are involved in energy metabolism. Mouse studies have demonstrated that the signaling molecules leptin and adiponectin control bone mass and energy metabolism through multiple mechanisms, including actions that affect the sympathetic nervous system (SNS) ([Karsenty and Oury 2010](#); [Kajimura et al. 2013](#); [Motyl and Rosen 2012](#)). Dr. Rosen's group is working with a mouse model that is deficient in brown fat—a tissue that consumes energy to regulate body temperature—to explore the connection between the SNS, bone, and brown adipose tissue ([Motyl et al. 2013](#)).

Anorexia nervosa in humans provides another context for studying the interactions between bone and fat. People who have anorexia nervosa are at increased risk of fracture due to low BMD, an elevated proportion of fat cells in their marrow, and below average amounts of brown adipose tissue ([Misra and Klibanske 2013](#)).

Translational implications for diabetes and bone health

Recent articles in the popular press have linked cold temperatures to weight loss. They are based on findings that energy-storing white fat can adopt the energy-burning properties of brown fat. The mechanisms that underlie this “browning” process, and strategies for engaging them, are receiving considerable attention by the research community. The change appears to be mediated by factors that influence the SNS: changes in brain chemistry due to an enriched environment, exposure to cold, medications that interfere with beta-adrenergic receptors (e.g., propranolol), and diabetes drugs that belong to the thiazolidinedione family.

Aging also is associated with diminished SNS activity, as well as with increased bone turnover in postmenopausal women ([Farr et al. 2012](#)). Another link between an elevated SNS response and fragility comes from the long-standing NIH-funded SOF: women who have an elevated resting heart rate (a marker of increased SNS activity) have an increased fracture risk ([Kado et al. 2012](#)).

Second generation antipsychotic medications, such as risperidone, are prescribed to treat conditions including schizophrenia, depression, and attention-deficit hyperactivity disorder. As the drugs are used more widely, researchers and health care providers are noting metabolic side effects such as weight gain and weak bones. Although the drugs may be detrimental to bone, their effects may be exacerbated if the patients already have poor bone health. Dr. Rosen's lab is exploring the mechanisms by which these drugs influence serotonin-mediated signaling and the beta-adrenergic response.

Dr. Rosen concluded by noting that bone remodeling does not occur in isolation. Its connection with energy metabolism suggests that targets for managing glucose control and type 2 diabetes remain to be discovered. The brain, via the SNS, mediates endocrine interactions between bone and fat. If drugs were to be developed that would encourage the conversion of white adipose tissue to energy-burning brown fat, researchers would need to be mindful that such compounds may also affect patients' skeletal health.

Discussion

Much of the discussion focused on the extent to which the mouse findings could be applied to humans.

Other questions related to how exercises that are known to build bone influence bone marrow fat. Although mechanical stimulation reduces marrow adiposity through the beta-catenin and PPAR-gamma signaling mechanisms ([Case et al. 2013](#)), many research questions remain unanswered.

ANNOUNCEMENTS

Two meetings are being planned for September 11 in conjunction with the American Society for Bone and Mineral Research annual meeting in Houston, Texas:

- [The ASBMR Symposium to Highlight the Effects of Diabetes and Disordered Energy Metabolism on Skeletal Health](#)
- [Mechanistic and Therapeutic Insights into Skeletal Biology Learned from the Study of Rare Bone Diseases](#) (organized by the National Bone Health Alliance, in partnership with the Rare Bone Diseases Patient Network)

American Bone Health will be managing the [Best Bones Forever!](#) program that the HHS Office of Women's Health had developed.

The NIAMS has developed 2014 [health planners](#) to make information about bones, joints, muscles, and skin more accessible to people from underserved racial and ethnic communities. The planners—which target African Americans; Hispanics/Latinos; Asian Americans and Pacific Islanders; and American Indians, Alaska Natives, and Native Hawaiians—are freely available while supplies last.