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MEETING REPORT

Bone and diabetes (Sun Valley 2013)

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There is a growing interest by the research community in the relationship between mechanisms regulating energy balance and bone homeostasis. Recent progress in unraveling this cross-talk is placing diabetes as a pathology which may further illuminate this connection. The goal of this session at the 43th Sun Valley Workshop was to review clinical and basic research evidence for considering of skeletal complications in diabetes as a distinctive pathology resulting from impaired regulation of energy balance.

Dr Ann Schwartz, Department of Epidemiology and Biostatistics, University of California San Francisco, presented studies in humans wherein evidence supports that diabetes has a negative impact on the boney skeleton. Meta-analyses show that those with Type 1 diabetes mellitus (T1D) or Type 2 diabetes mellitus (T2D) have a higher risk of fracture, particularly hip fracture, than those without diabetes. Bone mineral density (BMD) tends to be lower in T1D and higher in T2D, but both have higher fracture risk than would be expected from BMD. These data indicate that additional bone quality issues may be involved in making bones of persons with diabetes more susceptible to fracture. An important clinical implication of these findings is that prediction of fracture risk using BMD T-score or FRAX in individuals with diabetes may be compromised. Indeed, newer studies would suggest that T-scores and conventional FRAX calculations underestimate the risk of fracture in those with T2D. The reasons for increased risk of fracture in diabetics are not entirely clear. Published data indicate that contributing factors may include increased falls and diabetic complications. Bone quality may also be compromised in T2D. Studies support a role for decreased bone formation, increased sclerostin production, enhanced production of advanced glycosylation products, increased cortical porosity, and accelerated bone loss in the pathogenesis of diabetic bone disease. This presentation provides fertile thinking for future studies in the field. High priority areas identified for future studies are:

- What are the differences and similarities in clinical aspects of diabetic bone in T1D versus T2D?
- Are the imaging and other clinical results consistent with particular mechanisms for bone fragility? Do they rule in or out any mechanisms?
- What are the implications for prevention and treatment of osteoporosis in patients with diabetes?

Dr Laura McCabe, Department of Physiology and Radiology, Michigan State University, discussed the causal relationship between diabetic disease and a status of bone marrow stem cells, which leads to altered bone remodeling. She discussed the similarities and differences in the impact of T1D versus T2D on bone remodeling. Although T1D is associated with a decrease in bone mass, whereas T2D does not impact bone mass, both diseases affect bone quality leading to increased fracture risk. Both types of diabetic pathology result in decreased bone turnover. Two different contributing mechanisms were proposed: (1) dysregulation of glucose metabolism leading to the accumulation of reactive species (ROS, AGEs), which interact with bone matrix collagen and change biomechanical properties of bone leading to increased stiffness; and (2) changes in the bone marrow milieu of regulatory cytokines with increase in the proinflammatory factors causing apoptotic death of osteoblasts. Different animal models of T1D were discussed including the model of induced diabetes by streptozocin-mediated damage of insulin-producing pancreatic beta cells and the Akita mice, a model of spontaneous disease due to defect in proinsulin processing and maturation to active insulin. Both models showed decreased osteoblast number and bone formation with simultaneous increase in adipocyte number in the bone marrow. To test the hypothesis that decreased osteoblast number results from the alteration of fate of mesenchymal stem cells from osteoblasts to adipocytes, the experimental model of inhibition of marrow adipogenesis due to pharmacological blockage of PPARg activity was applied and showed that even in the conditions that inhibited adipocyte formation the decrease in osteoblast number and bone formation was still occurring. More detailed analysis showed that there is an increase in the production of proinflammatory cytokines, including tumor necrosis factor-α, which lead to suppression of Wnt10b expression in osteoblasts and increase in Caspase 3 activity. Wnt signaling is likely targeted in diabetic (type 1 and 2) bone disease, leading to detrimental changes in bone remodeling. The following issue was discussed:

- Is the rodent model appropriate for studying changes in human diabetic patients?

Dr John Fowlkes, Department of Pediatrics, University of Arkansas for Medical Sciences and Arkansas Children's Hospital Research Institute, shared studies examining the role that insulin and its homolog, insulin-like growth factor 1 (IGF-1), have on the boney skeleton, and provided data to show that both may have a role in improving diabetic bone disease. In humans with diabetes, endogenous insulin and IGF-1 correlate with BMD and bone formation markers, and decreased IGF-1 in diabetes has been shown to be associated with osteoporosis and increased fracture risk. Both the insulin receptor and the IGF receptor have an impact on skeletal development; however, the combined loss of both receptors has the most profound effect on skeletal development. Newer mouse models suggest that insulin and IGF-1 signaling may have overlapping as well as distinct roles in skeletal development. Molecular studies suggest that osteoblastogenesis is impaired from early stages of osteoblast commitment and may therefore explain the profound lack of new bone formation, compromised skeletal microarchitecture and diminished bone strength observed in T1D murine models. In murine models of T1D, insulin therapy is consistently capable of improving regenerative properties of the diabetic skeleton and many of the histomorphometric and biomechanical properties, as well as the molecular deficits of diabetic bone. IGF-1 therapy in T1D mouse models also improves regenerate bone formation, as well as improves skeletal resistance to fracture. Thus, animal models suggest that both insulin and IGF-1 may improve skeletal well-being in T1D. Future studies should examine:

- Do insulin and IGF-1 have unique roles in the pathogenesis and/or treatment of diabetic bone disease?
- Are the effects of insulin and/or IGF-1 on skeletal health in diabetes direct or indirect, or both?
- Is there a role for insulin and IGF-1 co-therapy to prevent or treat diabetic bone disease?
- Can skeletal cells become insulin resistant?

Dr Beata Lecka-Czernik, Department of Orthopaedic Surgery and Center for Diabetes and Endocrine Disease, University of Toledo Health Sciences Campus, presented studies indicating that secretory activities of highly metabolic beige fat have an anabolic effect on bone. Clinical evidence shows that insulin resistance and T2D are associated with increased fractures and that fat tissue involved in energy dissipation, known as brown adipose tissue (BAT), counteracts many if not all of the symptoms associated with T2D. It has been recently recognized that besides preformed BAT, adult humans may also possess so-called inducible BAT or 'beige' fat, the activity of which correlates negatively with impairment in energy metabolism seen with aging, diabetes and obesity; conditions which are also associated with a decrease in bone mass, an increase of fat volume in bone marrow cavity and an increase in fractures. On the other hand, high beige fat activity correlates positively with high bone mass in young women and adolescents. The hypothesis that energy metabolism regulates bone turnover has been tested in a murine model for induction of beige fat by ectopic expression of FoxC2 transcriptional regulator, specifically in adipocytes (FoxC2$^{+/Tg}_{AD}$ mice). FoxC2$^{+/Tg}_{AD}$ mice are lean, insulin sensitive and have high bone mass due to increased bone formation associated with high bone turnover. This bone phenotype is linked to the activation of endosteal osteoblasts, while osteocytes have decreased the expression of the SOST transcript encoding sclerostin and elevated the expression of RANKL. In a set of *in vitro* and *ex vivo* experiments, it has been demonstrated that adipocytes of beige phenotype secrete number of factors with anabolic activity on bone. Beige fat secretome activated the osteoblast gene markers in recipient marrow mesenchymal stem cells and increased the levels of pAkt and β-catenin, whereas in recipient osteocytes this activity decreased SOST expression. Analysis of beige fat secretome identified several factors with bone anabolic activity, among them IGFBP2, Wnt10b, adiponectin and BMP4. It has been concluded that relative to its location beige adipocytes may serve endocrine (if present in peripheral fat depot) or paracrine (if present in bone marrow) function, which is beneficial for the skeleton. The function of beige fat in regulation of bone mass represents a new paradigm of ties between bone and energy metabolism system. The following aspects of fat–bone cross-talk were discussed:

- Contribution of marrow fat vs peripheral fat to the maintenance of bone homeostasis.
- Is marrow fat metabolically active and contributes to the systemic energy balance?
- Can fat be a therapeutic target to treat osteoporosis?

The session concluded with a presentation by Dr Jason Inzana from the Department of Biomedical Engineering and Center for Musculoskeletal Research, University of Rochester Medical Center, who was a recipient of the Alice L. Lee Young Investigator Award. Dr Inzana presented a paper indicating that skeletally immature mice are more susceptible than mature mice to the detrimental effects of a high-fat diet (HFD) on cancellous bone in the distal femur. The study tested a hypothesis that cancellous bone is more susceptible to the detrimental effects of HFD before skeletal maturity and that removing excess fat from the diet will reverse these effects. Mice of two different ages were fed either HFD or low-fat diet (LFD) for 12 weeks. The HFD-fed immature mice (5 weeks old) had greater decreases in femoral trabecular bone volume fraction (BVF) than mature mice (20 weeks old). After switching the HFD-fed mice to a LFD for 12 weeks, the femoral BVF in immature mice showed no improvements, whereas the BVF of mature mice matched lean controls. Diet effects on vertebral strength and trabecular structure were similar between the age groups, with deficits after 12 weeks on the HFD and recovery to that of lean controls after diet correction. These data suggest that femoral cancellous bone is more susceptible to the detrimental effects of HFD before skeletal maturity and is less able to recover after diet correction.

The translational impact of this study consists of consideration of an impact of diet on the skeleton, specifically in adolescence.

In conclusion, the presenters developed a strong argument based on basic and clinical research that diabetes has a profound and negative impact on skeletal integrity. While much work is still needed to better understand the multifactorial

nature of the skeletal deficits associated with diabetes, newer intervention to improve bone health in these individuals may only be realized as underlying mechanisms emerge. One of these interventions may include induction in fat tissue of bone anabolic activities, which may regulate bone homeostasis in the endocrine/paracrine manner. It was proposed that the skeletal complications of diabetes be termed: diabetic bone disease.

Conflict of Interest

The authors declare no conflict of interest.