Summary of the Proceedings of the ASBMR Symposium: The Effects of Diabetes and Disordered Energy Metabolism on Skeletal Health

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The ASBMR Symposium on The Effects of Diabetes and Disordered Energy Metabolism on Skeletal Health was held on Thursday, September 11, 2014, one day prior to the ASBMR 2014 Annual Meeting, at the George R. Brown Convention Center in Houston, Texas, USA.

OVERVIEW

Fractures are a costly public health burden at the societal and individual level. In 2005 approximately 2 million fractures occurred in the U.S. among those ≥50 years old with an estimated treatment cost of $17 billion, projected to increase 50% by 2025. Fractures are a primary concern among adults aged 65 years or older, in whom the prevalence of T2DM mellitus (T2DM) is now greater than 25% in the U.S. Additionally, life expectancy has increased for patients with T1DM and many are living to an age when fracture risk becomes a concern.

Older adults with T2DM are on average overweight and have higher bone density than healthy peers. However, the higher bone mass does not confer protection against fractures. Indeed, the risk of hip fracture is increased by 40-70% in these individuals, and it is 6-fold higher in patients with T1DM, relative to individuals without diabetes; much higher than would be expected from their relatively modest reductions in bone density, pointing towards alterations of bone quality . Of note, fracture incidence is still increased after correcting for falls. Thus, morbidity from fractures, itself an important public health issue in the broader population of older adults, is more prevalent among those with diabetes who are also more likely to have difficulties with fracture healing and rehabilitation than non-diabetic subjects.

The clinical and basic science research community is increasingly interested in understanding the effects of diabetes and impaired energy metabolism on the skeleton. The ASBMR Symposium was designed to provide an opportunity for researchers to share insights and new findings across the barriers that often separate investigators involved with basic, translational and clinical research. The Symposium also aimed to catalyze inter-disciplinary interactions between researchers and clinicians interested in diabetes and those focused on bone health

To accomplish these goals, the Symposium was structured in four sessions: Advances in Understanding Insulin Resistance, Lessons from Pre-clinical Models of Diabetes and Bone, Human Metabolism in Diabetes, and Clinical Management. Brief summaries of the presentations in each session are provided below.

Several important themes emerged from this day.

- Advances in the understanding of insulin resistance and fat metabolism are highly relevant to the efforts to understand the effects of diabetes and disordered energy metabolism on the skeleton.
- New findings underscore the extensive cross talk between impaired energy metabolism and the skeleton.
- There are an increasing number of clues regarding the reasons for greater bone fragility with diabetes, but research into the underlying mechanisms remains an essential task. Themes highlighted in these talks included inflammation, greater cortical porosity, accumulation of advanced glycation endproducts, and reduced bone material strength.
- In the discussions, potential mechanisms and targets were noted that deserve further research attention, notably the effects of changes in vascular function, a hallmark of diabetes, on bone and the role of osteocytes in diabetic bone fragility.
- A more reliable prediction tool is essential for clinical care of diabetic patients. FRAX (with BMD) currently under-estimates fracture risk in T2D patients, but, with some adjustment, has the potential for more accurate prediction in this population.
- An integrated approach to fracture prevention in diabetic patients is needed that considers the effects of diabetes medications on the skeleton and the efficacy of osteoporosis therapies in those with diabetes. Such an approach will require additional clinical and basic investigation.
- There is increasing evidence from basic and clinical research that "diabetic bone disease" should be recognized as a distinctive pathology resulting from the effects of impaired regulation of energy balance on the skeleton.

SESSION I: ADVANCES IN UNDERSTANDING INSULIN RESISTANCE

Co-Chairs: Solomon Epstein, M.D., FRCP, Mount Sinai School of Medicine, USA and Beata Lecka-Czernik, PhD, University of Toledo College of Medicine, USA

A goal of Session I of this Symposium was to present to the bone research community recent state-of–the-art developments in understanding the pathogenesis of insulin resistance at the cellular and organismal levels.

An Epigenomic and Transcriptional Basis for Insulin Resistance

The presentation by Evan Rosen, M.D., Ph.D., from the Beth Israel Deaconess Medical Center introduced to the audience a concept of the epigenomic and transcriptional basis for development of cellular insulin resistance.

Insulin resistance is a major pathological feature of Type 2 diabetes, and is also seen in a wide variety of other conditions, ranging from lipodystrophy to sepsis to glucocorticoid excess. Many causal pathways have been elucidated, including ER stress, mitochondrial dysfunction, and defects in the insulin signaling pathway, that underlie at least some forms of insulin resistance. Surprisingly little attention, however, has been paid to defining common mechanisms of insulin resistance that are shared between disparate perturbations; such core pathways would be highly advantageous to target therapeutically. In his research, Dr. Rosen used a comparative model of insulin resistance in cultured adipocytes to identify oxidative stress as just such a core causal pathway[1]. One feature of all these pathways is their subcellular location in extranuclear sites, such as the cytosol, plasma membrane, or various organelles. There is mounting evidence, however, that nuclear (i.e. epigenetic and

transcriptional) pathways play a role in insulin resistance; this includes the use of PPAR-γ agonists as clinical insulin sensitizers, in addition to numerous demonstrations that fetal programming can affect insulin sensitivity later in life. To address this experimentally Dr. Rosen used genome-wide chromatin state mapping to identify *cis*-regulatory elements that are differentially enriched in adipocytes made insulin resistant with either dexamethasone (Dex) or TNF-α (TNF). These data enabled him to make predictions about transcription factors that may act as common determinants of insulin resistance.

He identified hundreds of adipocyte enhancers that are differentially regulated by Dex and TNF, including a handful that displays concordant activation in response to these two very different pharmacological stimuli. Motif finding in these regions suggests the involvement of the glucocorticoid receptor (GR) and the vitamin D receptor (VDR). The GR is expected as a downstream regulator of Dex action, of course, but its role in TNF signaling seems paradoxical. In fact, he showed that TNF activates the GR in a partially ligand-independent fashion, causing nuclear translocation and DNA binding. Knockdown of GR blocks both Dex- and TNF-induced insulin resistance. ChIP-seq reveals that TNF directs the GR to a subset of binding sites controlled by Dex; the genomic determinants of this specificity are currently being probed. The VDR is an unexpected candidate to cause insulin resistance, given the inverse association reported between serum vitamin D levels and insulin sensitivity. In fact he showed that overexpression of VDR causes insulin resistance in adipocytes, while knockdown of VDR has the converse effect. Furthermore, vitamin D ligand does not enhance or reverse this action of the VDR, and a ligand-binding mutant form of VDR is still able to cause insulin resistance.

Finally, he identified several GR and VDR target genes that participate in insulin resistance. These genes are all bound and induced by both GR and VDR, are all elevated in the adipose tissue of obese, insulin resistant animals, and cause insulin resistance when overexpressed in vitro. Taken together, he demonstrated a use epigenomic mapping to predict and then validate a novel transcriptional network controlled by two nuclear hormone receptors with a profound impact on cellular insulin sensitivity.

In ongoing studies, Dr. Rosen is looking at epigenomic changes in the isolated adipocytes of human subjects across a wide range of insulin sensitivity. While these studies are still in their early phases, he can already identify many enhancers that differ in activity according to the degree of insulin resistance. He believes that these studies will eventually lead to identification of causal pathways in human metabolic dysfunction, and serve as a template that can be used to identify novel transcriptional pathways in many areas of biomedical research.

Discussion: An audience member asked if visceral fat and marrow fat develop insulin resistance by similar mechanisms involving GR and VDR. The presenter pointed to the necessity to perform such studies and difficulties in obtaining sufficient quantities of these tissues from humans for genome screening. Another comment was in regards to normal insulin sensitivity in children with vitamin.D-resistant rickets disease. Dr. Rosen commented that the role of VDR in development of insulin resistance is ligand independent whereas vitamin D-resistant rickets disease is ligand dependent. The discussion also included a comment on the need to study the relationships among GR, VDR and NF-kappaB, all three signaling pathways of high importance for maintenance of bone homeostasis.

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Adipose Tissue, Insulin Resistance and Systemic Metabolic Flexibility

The presentation by Philipp E. Scherer, Ph.D. from Touchstone Diabetes Center at the University of Texas Southwestern Medical Center focused on the role of adipose tissue in the development of insulin resistance and regulation of systemic metabolic flexibility.

During the progression from the lean to the obese state, adipose tissue undergoes hyperplasia as well as hypertrophy in an attempt to cope with the increased demand for triglyceride storage. This requires a high degree of plasticity at both the cellular and at the tissue level. The extracellular matrix of adipose tissue faces unique challenges with respect to adjusting to the need for remodeling and expansion. In parallel, the vasculature has to adapt to altered requirements for nutrient and oxygen exchange.

A decrease in the plasticity of these processes leads to metabolic dysfunction. Furthermore, to maintain a healthy, non-inflamed phenotype, complex regulatory mechanisms are in place to ensure adipocytes and stromal vascular cells efficiently crosstalk to allow adipose tissue to expand upon increased demand for storage of triglycerides. Dr. Scherer proposed a model of stepwise adipose tissue dysfunction that is initiated by rapid expansion of existing adipocytes to accommodate triglycerides during excess caloric intake. This leads very quickly to an acute, and eventually chronic, state of hypoxia in adipose tissue. Changes during the expansion process also affect adipocyte-derived secretory factors (adipokines), such as adiponectin. Adiponectin promotes insulin sensitivity, decreases inflammation and promotes cell survival. Its levels are frequently downregulated in the obese state. Avoiding the obesity-associated downregulation of adiponectin in fact allows the adipose tissue to further expand. This leads to a "healthy" expansion, with enlarged subcutaneous adipose tissue, improved vascularization and enhanced adipogenesis. As a result, we have improved systemic insulin sensitivity. However, Dr. Scherer also emphasized the beneficial role of mild local inflammation for preservation of insulin sensitivity in adipocytes.

These phenotypes of healthy adipose tissue expansion have a positive effect on the systemic lipotoxic environment that prevails in the obese state. This may be particularly relevant for sphingolipids that tend to accumulate and prompt a high level of cytotoxicity under high fat diet conditions. Indeed, high plasma ceramide levels correlate with insulin resistance. Adiponectin potently stimulates a ceramidase activity associated with its two receptors, adipoR1 and adipoR2, and enhances ceramide catabolism and formation of its anti-apoptotic metabolite – sphingosine-1-phosphate (S1P), independently of AMPK. These observations suggest a novel role of adipocyte-derived factors that have beneficial systemic effects, with sphingolipid metabolism as its core upstream component.

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The Regulation of Glucose Metabolism by Bone and Its Implication

The presentation by Gerard Karsenty, M.D., Ph.D. from Columbia University Medical Center provided evidence indicating that bone is an organ regulating systemic glucose metabolism and that osteoblast differentiation is glucose dependent.

It was recently shown that bone is an endocrine organ and that one of the hormones secreted by osteoblasts, osteocalcin, is a regulator of glucose metabolism in part because it favors insulin secretion. These observations were verified genetically in humans. It was further shown that in turn insulin signals back to osteoblasts so that in a feed forward loop it increases the bioactivity of this hormone. Taken as a whole these observations raise a series of novel questions. Chief among them is to know whether bone is a site of insulin resistance in animals with type 2 diabetes. A second question is to determine if bone contributes to the glucose intolerance often observed in obese animals and humans.

To address these two questions Dr. Karsenty evaluated the consequences of an osteoblast-specific overexpression or of a loss of insulin receptor expression in mice fed a high fat diet (HFD). He determined that the severity of glucose intolerance and insulin resistance that mice develop when fed a HFD is a consequence of osteoblast-dependent insulin resistance. Insulin resistance in osteoblasts led to a decrease in circulating levels of the active form of osteocalcin, thereby decreasing insulin sensitivity in skeletal muscle. Insulin resistance developed in osteoblasts as the result of increased levels of free saturated fatty acids, which promote insulin receptor ubiquitination and subsequent degradation. Together, these results underscore the involvement of bone, among other tissues, in the disruption of whole-body glucose homeostasis resulting from a HFD and the involvement of insulin and osteocalcin cross-talk in glucose intolerance. Furthermore, these data indicate that insulin resistance develops in bone as the result of lipotoxicity-associated loss of insulin receptors.

Another question raised by the regulation of glucose metabolism by bone, is to elucidate what could be the reasons for the existence of such a regulation. To address this latter question he asked what are the functions of glucose in osteoblasts. Dr. Karsenty showed evidence that, for the most part, glucose uptake occurs in an insulin-independent manner in osteoblasts through the glucose transporter Glut1. Analysis of Glut1 function during development and after birth showed an unexpected synergy between glucose uptake in osteoblasts and osteoblast differentiation. This synergy relies on several molecular pathways including AMPK signaling, independently of Runx2 and insulin signaling.

Discussion: Questions included whether Runx2-induced osteoblast differentiation is attenuated with decreased glucose uptake and whether bone phenotype of Runx2 deficient embryos can be normalized by increasing blood glucose levels.

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SESSION II: LESSONS FROM PRECLINICAL MODELS OF DIABETES AND BONE

Co-Chairs: Roberto Fajardo, Ph.D., University of Texas Health Center, San Antonio, USA and John Fowlkes, M.D., University of Arkansas for Medical Sciences, USA

Skeletal Phenotype of Preclinical T1DM Models: Mechanisms Underlying Reduced Bone Formation

The presentation by Laura McCabe, Ph.D. from Michigan State University presented information from rodent models on the skeletal phenotype in Type 1 (or insulin dependent) diabetes and the mechanisms underlying reduced bone density.

Type 1 diabetes is a chronic medical condition that is associated with a number of complications that affect organ systems such as the eye, kidney and nervous system. Recent data now suggests that those with Type 1 diabetes are also at risk for developing skeletal complications that include low bone density and increased fracture risk. Such risk of poor bone health can negatively impact patient quality of life and increase health care costs for this group of individuals. To optimize therapies to treat and prevent bone loss associated with Type 1 diabetes, it is important to understand mechanisms at play in the pathological process. Dr. McCabe presented a brief review of pharmacologic (i.e., streptozotocin) and spontaneous (non-obese diabetic; NOD) Type 1 diabetic mouse models and their resulting bone phenotype. The phenotype in both diabetic mouse models shows decreased bone formation and low bone turnover; this response was noted to be similar to what is currently known about Type 1 diabetic bone disease observed in humans.

Dr. McCabe presented several aspects of her work which has explored possible molecular and cellular mechanisms accounting for decreased bone formation. First, bone marrow composition appears to influence bone metabolism in the T1D models. However, there was little indication that stem cell lineage allocation shifts towards adipocytes and away from osteoblasts were an important contributing factor. Instead, her lab has found that systemic and bone inflammation (such a TNF-alpha) plays a critical role in bone metabolism. One pathway for the influence of inflammation on bone appears to be alterations in Wnt signaling, suggesting a role of Wnt in this pathology. Dr. McCabe also presented promising pre-clinical data showing that intermittent PTH may have a role in the treatment of Type 1 diabetic bone disease.

Discussion: Comments focused on potential treatment options and appropriate animal modeling of pre-clinical therapeutics.

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Fat Metabolic Status and Bone

The presentation by Beata Lecka-Czernik, Ph.D. from the University of Toledo Health Sciences Campus, discussed what is known about fat metabolism and its impact on the skeleton.

Because fat tissue actively stores and dissipates energy, it is an essential contributor to the systemic regulation of energy metabolism. Advances in our understanding of the origins, functions, and pathophysiological consequences of fat tissue metabolism have prompted new research efforts exploring how fat metabolism can impact bone homeostasis. Fat tissues may serve different functions, depending on the type of fat as well as its location or "depot". Based on cell respiratory activity, which is associated with the number and activity of mitochondria in fat cells, fat tissue can be categorized into either white adipose tissue (WAT), which functions to store energy, and brown adipose tissue (BAT), which functions in energy dissipation. Most recently, a third category of "beige" fat, which has BAT-like activity and is located within WAT depots, has been identified and characterized for its role in energy dissipation and function in glucose metabolism.

Dr. Lecka-Czernik presented overviews and data about the poorly understood role of bone marrow adipose tissue (BMAT), which has characteristics of both WAT and BAT (similar to "beige" fat), in bone homeostasis. The location and pattern of BMAT distribution within the bone marrow cavity suggest that BMAT may have specific functions in modulating bone remodeling and hematopoiesis. BMAT responds to physiologic and pathologic changes in systemic energy metabolism by changing its volume and metabolic activity. Mouse models suggest that impairment in the amount and function of extra-medullar WAT, which occurs in diabetes, correlates with decreased bone biomechanical quality and increased fractures. Interestingly, this decline in WAT function is associated with increased fat accumulation in bone marrow and loss of the BAT-like characteristics of BMAT, overall suggesting a positive correlation between the BAT-like metabolic profile of BMAT and bone quality. On the other hand, improved energy metabolism and increased activity of BAT correlates positively with increased bone mass and attenuated fat accumulation in bone. Newly published data from Dr. Lecka-Czernik's lab shows that beige fat activity can have a positive effect on bone mass due to (at least in part) secreted factors that are osteo-promoting agents, such as Wnt10b and BMP4.

Discussion: Comments considered the evolving evidence that fat metabolic status and its endocrine/paracrine activities can regulate bone homeostasis.

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Role of the Skeleton in Insulin Signaling and Glucose Homeostasis

The presentation by Stavroula Kousteni, Ph.D. from Columbia University Medical Center described evidence for a new osteoblast secreted protein that modulates the interaction between the skeleton and energy metabolism.

Efforts over the last five years have demonstrated that the skeleton is an endocrine organ regulating glucose metabolism and energy expenditure. To date, osteocalcin has been the only known bone-derived hormone linking the skeleton to energy metabolism. Osteocalcin is an osteoblast-specific protein which when undercarboxylated favors insulin secretion and sensitivity. During her presentation, Dr. Kousteni presented results that establish the existence of a second osteoblast secreted protein, named Bone Protein 2, which modulates the skeleton-energy metabolism interaction. Because of contractual constraints, the identity of this protein could not be provided at the time of the meeting but should be made public in the near future.

Dr. Kousteni presented the sequence of experiments that led to the discovery of BP2 and its roles in energy metabolism and appetite control. These experiments showed that osteoblast ablation in mice resulted in hypoinsulinemia, hyperglycemia, glucose intolerance and insulin resistance. Moreover, osteoblast ablation decreased gonadal fat and increased energy expenditure and appetite. The decrease in fat, and the increase in energy expenditure, are opposite to the changes observed in Osteocalcin-deficient mice. In addition, appetite is not regulated by osteocalcin since osteocalcin-deficient mice have normal food intake and exogenous osteocalcin administration in mice with ablated osteoblasts did not suppress the increase in appetite. These observations provided the first experimental indication that, in addition to osteocalcin, other osteoblast-derived hormones may contribute to the function of the skeleton as a regulator of energy metabolism.

The identification of BP2 ultimately occurred after experiments were conducted with mice lacking FoxO1, an inhibitor of osteocalcin carboxylation. FoxO1 was specifically deleted in osteoblasts (FoxO1osb-/-). Increased osteocalcin bioactivity in FoxO1osb-/- improved glucose metabolism and this increase was greater than in enterococal surface protein (Esp) knockout mice that also exhibit increased osteocalcin activity. The search for additional proteins secreted by osteoblasts in FoxO1osb-/- mice revealed BP2, which is found in serum and bone. BP2 deletion in bone concomitantly decreases serum levels. Moreover, deletion of this osteoblast-secreted hormone in mice results in hyperglycemia as well as decreased insulin levels and beta cell numbers. Deletion also causes an increased accumulation of fat mass and appetite. Further evidence presented suggests that BP2 modulates appetite through hypothalamic signaling, an interaction that is independent of leptin. Administration of exogenous BP2 to BP2 knockout mice restores insulin activity in muscle tissue, normalizes glucose levels, and restores normal appetite.

Discussion: One audience member inquired as to the role of osteocytes in energy metabolism. At this time it is still unclear what role osteocytes play in energy metabolism and whether they express BP2.

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Effects of Advanced Glycation End Products on Bone

The presentation by Deepak Vashishth, Ph.D. from Rensselaer Polytechnic Institute discussed the effects of advanced glycation endproducts on bone collagen material properties and on bone cells.

The collagen network in bone is a key contributor to bone quality because it provides resistance against fracture but this protein is a key target of advanced glycation endproducts (AGEs). These AGEs accumulate as a result of post-translational modifications of type I collagen and result in covalent, glucose-derived crosslinks within and between fibers. The reactions that cause AGEs to form occur during normal aging and are accelerated by diseases such as diabetes. Dr. Deepak Vashishth presented results from numerous studies that demonstrate the impact of AGEs on bone toughness and energy dissipation, bone cell behavior, and the heterogeneous distribution of these glycation endproducts in bone tissue. His research collectively points to AGEs as a major factor underlying diabetic fragility fractures.

Glycated bone tissue fails at lower strains and thus has decreased fracture toughness. Experimental evidence shows linear microcracks preferentially develop in highly glycated bone tissue whereas diffuse damage microcracks more commonly develop in bone tissues with less AGEs. This is an important difference because energy dissipation is greater with diffuse damage than linear microdamage. The presence of AGEs, and therefore microdamage, is not uniform in bone tissue. Dr. Vashishth showed evidence indicating that AGEs accumulate more in trabecular than cortical bone, the former having greater surface area exposure for circulating sugars. This result is somewhat surprising since trabecular bone has higher metabolic activity and remodeling resets AGE content in bone tissue to zero. However, AGEs also inhibit bone cell behavior, suppressing osteoclastic resorption and thereby limiting the beneficial effects of remodeling. This latter point is important within the context of diabetes, where the effect of AGEs on bone cells is in addition to the inhibitory effects of hyperglycemia on osteoblasts and osteoclasts.

Finally, data were presented showing the potential of N-phenacylthiazolium bromide as an AGE crosslink cleaving therapy.

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SESSION III: HUMAN BONE METABOLISM IN DIABETES

Co-Chairs: Mary L. Bouxsein, Ph.D., Harvard Medical School, Boston, Massachusetts and Nicola Napoli, M.D., University Campus Bio-Medico, Rome, Italy

Biochemical Markers: Novel Regulators of Bone Metabolism in Diabetes

The presentation by Mishaela Rubin, M.D. from Columbia University Medical Center provided an update on biochemical markers as potential regulators and predictors of bone fragility in diabetic patients.

There is considerable evidence that adults with type 2 diabetes mellitus (T2D) have an increased risk of fracture, despite increased body mass index and normal to high bone mineral density (BMD). The factors underlying increased fracture risk in T2D remain to be identified, and biochemical markers may provide important mechanistic insights and may also improve prediction of fracture risk. Dr. Rubin reviewed several clinical studies of biochemical markers of bone turnover that have reported reduced bone turnover in T2D, with a disproportionate reduction in bone formation. Specifically, studies have reported lower serum osteocalcin and procollagen type 1 N-terminal propeptide (P1NP) levels in patients with T2D along with a tendency towards lower PTH levels. In fact, in one study, the combination of low PTH and low osteocalcin predicts vertebral fracture risk independent of lumbar spine BMD. The levels of bone resorption markers in T2D are less consistent, with data showing either no difference or reduced bone resorption markers in patients with T2D. In addition, Dr. Rubin noted that although limited, histomorphometric analysis of iliac crest biopsies shows reduced bone formation in T2D, with reduced mineralizing surface, bone formation rate and osteoblast surface.

Dr. Rubin then reviewed evidence for other biomarkers that may contribute to skeletal fragility in T2D. In the past 3 years several studies have reported increased serum levels of sclerostin, the osteocyte product that inhibits the anabolic Wnt β-catenin pathway, in T2D. It is unclear, however, whether these serum markers may reflect osteocyte activity at the tissue level. Nonetheless, Dr. Rubin hypothesized that there may be a

derangement in mechano-sensation in T2D. Low IGF1 levels are also associated with increased risk of vertebral fractures in T2D independent of BMD.

An additional potential mechanism underlying skeletal fragility in T2D may be alteration in collagen cross-linking and the accumulation of advanced glycation end-products (AGEs) in the organic bone matrix. Although AGEs accumulate slowly in tissues during aging, they are markedly increased in patients with diabetes, forming non-enzymatic cross-links within and across collagen fibers. In contrast to normal enzymatic cross-linking in collagen which gives bone its toughness and scaffolding properties, AGEs are associated with more brittle bone that is less able to deform before fracturing. Higher urinary pentosidine levels are associated with an increased prevalence of vertebral fractures and an increased risk of incident clinical fractures among those with T2D independent of BMD. Finally Dr. Rubin showed evidence that serum levels of the AGE carboxy-methyl-lysine (CML) are associated with risk of hip fracture.

In conclusion, several biochemical markers are altered and may shed light on the pathophysiology of skeletal fragility in T2D. However, there is insufficient evidence to recommend routine use of biochemical markers for prediction of fracture risk in T2D. Furthermore additional studies are needed to determine whether these biomarkers could enhance routine diabetes care.

Discussion: A key question that was raised is whether the interpretation of serum CTX measurements in T2D needs special attention due to the alterations in the collagen cross-link profile seen in T2D.

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Beyond DXA: Imaging in Diabetes

The presentation by Thomas Link, M.D., Ph.D. from the Department of Radiology and Biomedical Imaging at the University of California at San Francisco reviewed recent studies using advanced imaging techniques to identify skeletal abnormalities in individuals with T2D.

Dr. Link reminded the group that epidemiological studies have found that patients with type 2 diabetes mellitus (T2D) have a higher incidence of fragility fractures despite normal or elevated bone mineral density (BMD) measured with DXA. One inference from these studies is that *bone quality* factors independent of BMD may contribute to the risk of fragility fractures in T2D. Dr. Link noted that DXA-derived trabecular bone score (TBS) of the spine is a textural measurement that has been shown to be lower in those with T2D, and also to predict fracture in T2D independently of BMD. High resolution quantitative computed tomography (HR-pQCT) is a relatively new technology capable of directly and non-invasively assessing cortical and trabecular bone microstructure at the distal radius and distal tibia. Dr. Link showed work from his group, using HR-pQCT, indicating that postmenopausal women with T2D and a history of fragility fracture have increased cortical porosity compared to women with T2D and no prior fracture. This study provided evidence for the key importance of cortical abnormalities in the increased prevalence of fragility fractures in T2D patients and the potential role of HR-pQCT as a novel diagnostic imaging test measuring cortical porosity. Of note, however, while prior work had shown increased cortical porosity in postmenopausal women with T2D versus controls, the more recent study by Patsch et al only found increased cortical porosity in T2D patients with prior history of fracture. Additional work is needed in larger cohorts to determine if cortical porosity is a feature of T2D, to understand the causes of higher cortical porosity in T2D, and to assess whether porosity depends on disease duration, disease severity and/or other factors. Although not yet published, it was noted that an abstract was being presented at the main ASBMR meeting reporting increased cortical porosity associated with T2D in the Framingham cohort of older women and men.

Dr. Link also showed his group's work using MR spectroscopy of the spine to demonstrate that patients with T2D have altered bone marrow fat. Furthermore, vertebral bone marrow fat content was positively correlated with HbA1c and visceral adipose tissue in T2D patients, whereas decreased unsaturated bone marrow lipids were associated with T2D and fragility fractures.

In summary, this lecture showed that novel imaging techniques have been used to identify aspects of bone structure and bone marrow composition that are altered in those with T2D, particularly in those with T2D and a history of fragility fracture. Future studies using these imaging technologies may provide additional insights into the pathophysiology and morphological correlates of increased bone fragility in T2DM patients.

Discussion: Focused on challenges in assessing cortical porosity and interpreting alterations in bone marrow lipid profiles.

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Bone Material Properties in Type 2 Diabetes: Is Skeletal Deterioration Another Diabetic Complication?

The presentation by Sundeep Khosla, M.D. from Mayo Clinic Rochester, Minneapolis focused on clinical evidence for altered bone material properties in diabetes.

There is growing evidence that despite having higher BMIs and areal BMD by DXA, patients with type 2 diabetes (T2D) are at increased fracture risk. Dr. Khosla notes that these observations have led to the hypothesis that T2D results in compromised bone "quality" (i.e., bone material strength and/or bone microarchitecture) that leads to the increase in fracture risk. He reviewed a recent study where his group formally tested this hypothesis in 60 normal postmenopausal women, 30 with T2D for > 10 yrs and 30 age-matched, non-diabetic controls. An index of cortical bone material properties (bone material strength index, BMSI) at the midshaft of the tibia was obtained using a hand-held microindentation instrument (Osteoprobe, Active Life Scientific). BMSI was significantly lower (by 12% unadjusted, $P < 0.001$, and by 11% adjusted for BMI, $P < 0.001$) in the T2D patients as compared to the non-diabetic controls. By contrast, BMD by DXA tended to be higher in the T2D patients. Cortical porosity by HRpQCT also tended to be increased in the T2D patients, but none of the other trabecular or cortical parameters were significantly different between the groups. The mean glycated hemoglobin over the previous 10 yrs was negatively correlated ($r = -0.41$, $P = 0.026$) with the BMSI, indicating that worse glycemic control was associated with poorer BMSI. In terms of safety of the microindentation instrument, Dr. Khosla reported that they observed no complications in over 60 subjects who have undergone the procedure (i.e., stress fractures, pain, infection, etc), perhaps related to the fact that the indentations are miniscule (< 200 µm). These findings represent the first demonstration, using a direct *in vivo* index of bone material strength, of compromised bone material properties in patients with T2D. Particularly given the relationship of the BMSI with chronic glycemic control, Dr. Khosla suggested that skeleton should be recognized as another important target tissue subject to diabetic complications.

Discussion: Noted the potential challenges of making in vivo indentation measurements in individuals with high BMI and high soft tissue thickness. There was also the suggestion that when investigating the deleterious effects of diabetes on the skeleton investigators should consider other drivers besides hyperglycemia and insulin resistance.

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SESSION IV: CLINICAL MANAGEMENT

Co-Chairs: Christian Meier, M.D., University Hospital Basel, Switzerland and Clifford Rosen, M.D., Maine Medical Center, USA and

New Diabetes Treatment and Bone

The presentation by Christian Meier, M.D. from the University Hospital Basel was focused on the effect of oral anti-diabetic drugs, particularly recently introduced drugs, on skeletal health.

Oral anti-hyperglycemic therapies most commonly used in patients with insulin-independent diabetes mellitus include drugs that stimulate insulin secretion (sulfonylureas, incretin-based therapies), insulin-sensitizers (metformin, thiazolidinediones) and drugs that increase glucose excretion in the urine (SGLT2-inhibitors).

Dr. Meier summarized preclinical and clinical data providing evidence that thiazolidinediones (TZDs) have a negative effect on bone with imbalanced bone turnover, bone loss and increased fracture risk. TZDs are insulin-sensitizing drugs that are agonists of peroxisome proliferator-activated receptor (PPARγ), a nuclear transcription factor that is expressed in bone marrow stromal cells, osteoblasts and osteoclasts. Activation of PPARγ2 affects the differentiation of mesenchymal stem cells with a shift in the flow of mesenchymal precursor cells from osteoblastic to adipogenic lineages thereby increasing adipogenesis at the expense of osteoblasts. Furthermore, TZDs have been shown to excert a pro-osteoclastic effect via activation of PPARγ1, expressed in osteoclasts. Based on randomized clinical trials and observational studies long-term TZD use has been associated with increased risk of non-vertebral fractures, particularly in women. Dr. Meier has pointed out that fracture risk is predominantly increased in TZD long-term users. However, data from a recent randomized-controlled study indicate that the detrimental effect on bone is limited to the time of TZD exposure with attenuation of bone loss after cessation of TZD treatment.

In contrast, metformin has been shown to induce osteoblast differentiation via activation of the AMPK signaling pathway with increased Runx2 expression. Clinical studies on the effect of metformin in humans are limited. Nevertheless, metformin treatment in postmenopausal women with type 2 diabetes did not show an effect bone turnover or bone mass. Observational studies suggest that metformin decreases fracture risk.

Of interest are recent data that Dr. Meier presented regarding the effect of incretin-based therapies which appear to have a protective effect on bone beyond improved glycemic control. Incretins (GIP, GLP-1, GLP-2) are

released by intestinal endocrine cells in response to nutritional intake. They are known to directly (GIP, GLP-2) or indirectly (GLP-1) regulate bone resorption after eating. Evidence of incretin effects in humans are confirmed in women exposed to exogenous GLP-2 resulting in a decrease of nocturnal bone resorption with a shift the overall bone turnover balance in favor of bone formation with a net increase in BMD. Preclinical studies indicate that incretin-based therapies (GLP-1 receptor analogs, DPP4-inhibitors) have beneficial effects on bone mass and protective effects on bone quality. Human data are limited and further clinical studies are certainly needed to clearly determine the effect of incretins and DPP-4 inhibitors on bone metabolism. Dr. Meier concludes that incretin-based antidiabetic therapies could prove to be ideal treatment options in type 2 diabetic patients with high fracture risk due to their bone sparing potential and due to their low risk of hypoglycemia thereby reducing fall and fracture risk.

Finally, he summarized data on the effects of SGLT2- inhibitors on bone. Sodium-glucose co-transporters (SGLT) are responsible for renal glucose reabsorption with SGLT2 accounting for app. 90% of re-absorbed glucose. SGLT2-inhibitors (canagliflozin, dapagliflozin) increase urinary glucose excretion and improve glycaemic control in type 2 diabetics. Data on the effect of SGLT2-inhibitors on bone metabolism are scarce; in a recent randomized, placebo-controlled trial no adverse effects of dapagliflozin on calcium metabolism, bone turnover or bone mineral density could be identified. However, the FDA filing for canagliflozin included a report of excess fractures in the treatment arm although the difference was not statistically significant.

Discussion: Comments focused on the need for individual assessment in prescribing oral anti-diabetic drugs for patients with high fracture risk.

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Identifying Diabetic Patients at High Risk of Fracture

The presentation by William Leslie, MD, University of Manitoba, Canada, focused on the diagnostic utility of various methods to identify diabetic patients at high risk of fracture.

Diabetes mellitus (both type 1 [T1D] and type 2 [T2D]) is an independent risk factor for fracture. This is partially mediated through reduced bone mineral density (BMD) in T1D, but does not explain the mechanism of T2D which is associated with preserved (or even increased) BMD.

Dr. Leslie noted that there is a paucity of methods to accurately predict fracture risk in older adults with T2D as a consequence of the BMD-fracture paradox in T2D. Cortical porosity from high-resolution peripheral QCT and material properties from micro-indentation analysis provide important insights into the pathophysiology of skeletal failure but are not routine clinical methods. Risk factors for osteoporotic fractures in the general population are also risk factors in those with diabetes. Dr. Leslie showed that of the independently validated risk assessment tools, only QFracture (United Kingdom) explicitly includes diabetes (stratified as T1D or T2D) as an entry variable. The WHO FRAX tool stratifies fracture risk in those with diabetes, but the risk is underestimated even after the effect of competing mortality is considered. Approaches and challenges in including diabetes information in FRAX and other algorithms were discussed.

Identifying high risk diabetic patients who fail to meet conventional treatment thresholds requires enhanced methods for risk assessment. Trabecular Bone Score (TBS), derived from lumbar spine DXA texture, and a biomechanical approach based upon load to strength ratios (i.e., factor-of-risk) appear promising. In FRAX, use of the rheumatoid arthritis category for T2D is a practical option that is being tested with data from the Manitoba cohort.

Dr. Leslie recommended that, at present, individuals with diabetes who have a prior fragility fracture (especially hip or vertebral) or osteoporotic BMD T-score or who are otherwise exceeding (or approaching) the treatment thresholds for the general population should be considered at high risk for fracture.

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Options for Pharmacological Treatment of Osteoporosis in the Patient with Diabetes -Currently Available Therapies

The presentation by Clifford Rosen, M.D. from Maine Medical Center Research Institute in Scarborough, Maine focused on pharmacological treatment for osteoporosis with currently available medications in the setting of diabetes mellitus, type 1 and type 2.

Dr. Rosen re-emphasized the utility of performing risk profiling to determine who to treat and when. He also reinforced the studies presented by Dr. Meier showing potential risks associated with the thiazolidinediones, and the possible protective effects of metformin. Moreover, Dr. Rosen presented data from CAMOS showing that many fewer diabetics with osteoporosis were treated compared to non-diabetics with the same risk factors.

Dr. Rosen noted particular difficulties for the provider and diabetic patient in determining the best approach to osteoporosis therapy including: 1) There are few data sets for patients with either type of diabetes testing efficacy of currently approved drugs for osteoporosis. 2) Low bone mass is almost universal in those with long standing T1D, yet timing of intervention is problematic particularly since these individuals are already on multiple drugs and intensive glucose monitoring. 3) There is significant uncertainty about the risk or benefit of concomitant anti-diabetic agents with respect to skeletal effects. 4) With the advent of powerful anti-resorptives, there is lingering concern that patients with diabetes may be at greater risk of subtrochanteric fractures.

In respect to treatment options, a point emphasized several times was that the number of subjects in randomized trials for osteoporosis drugs is extremely low for T1D and very low for T2D, thereby making the assessment of benefit or risk in the diabetic patient somewhat tenuous. There are small studies with under 30 subjects showing that bisphosphonates can increase bone mass in diabetics to the same extent as in non diabetics. Similarly in the Fracture Intervention Trial, there does not appear to be a difference in responsiveness to alendronate in respect to bone density changes. In the MORE trial of raloxifene diabetics also showed a significant risk reduction for vertebral fractures that was comparable to non-diabetics. Studies with anabolic agents including PTH and the monoclonal antibody to sclerostin have been confined only to animal work. A key unanswered question is whether there are distinct advantages to particular therapies (e.g. anti-resorptive vs anabolic). In summary, it was clear that more randomized trials are needed in patients with T1D and T2D at high risk of fracture to fully understand the potential spectrum of therapeutics that could be offered.

Dr. Rosen finished by reinforcing the importance of basic studies to define the mechanisms of diabetic bone disease and thus guide the use of potential therapeutics.

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Options for Pharmacological Treatment of Osteoporosis in the Patient with Diabetes - Novel Therapies

The presentation of Sophie Jamal, M.D. from the University of Toronto, Canada centered on the potential for use of new osteoporosis therapies to treat diabetic patients.

Dr. Jamal re-emphasized the extent of the clinical problem and the dilemmas facing clinicians who see patients with osteoporosis and diabetes. Potential novel treatments that are specific to the underlying mechanism of increased fracture risk in type 2 diabetes were reviewed and included: 1) the sclerostin monoclonal antibody which has been shown to increase bone formation markers, decrease bone resorption markers, and increase

BMD in healthy men and postmenopausal women; and 2): organic nitrates which also increase bone formation markers, decrease bone resorption markers and preferentially increase cortical bone parameters.

She showed data from her randomized trial of nitrates that revealed a significant improvement in bone mineral density and favorable changes in bone markers. In addition Dr. Jamal discussed the potential role of improved glycemic control and techniques to decrease fall risk in decreasing fractures in men and women with diabetes.

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