

**38<sup>th</sup> Sun Valley Workshop on Skeletal Tissue Biology, Aug 3-6, 2008**  
**Summary of Session: Bone as an endocrine organ**

This session featured four presentations, each of them covering different aspects of skeletal involvement in the regulation of energy metabolism. The main objective of this session was to demonstrate that bone is an integral part of the energy metabolism endocrine network. Metabolic cross-talks between Bone-Brain, Bone-Fat, Bone-Pancreas, Bone-Guts, and Bone-Muscle, were discussed as well as a possible role of the circadian system in coordinating metabolic communication between bone and other organs.

In the presentation “Local and systemic functions of bone fat and its contribution to the energy metabolism; The effect of diabetes and obesity on bone”, Dr. Lecka-Czernik discussed possible metabolic interactions between bone fat and other organs, which are a part of the energy metabolism system. Evidence has shown that bone marrow adipocytes express a set of proteins like those of other fat deposits involved in lipid and carbohydrate metabolism. In addition, marrow fat produces adipocyte-specific hormones such as leptin, adiponectin and resistin, which determine cellular insulin sensitivity. Moreover, bone marrow adipocytes respond to the anti-diabetic, insulin sensitizing drugs, TZD, with increased expression of genes involved in the insulin signaling and fatty acid metabolism, but not glucose metabolism. This suggests that bone marrow adipocytes are insulin sensitive and are involved in fatty acid-dependent energy metabolism, but may not be involved in insulin-dependent glucose metabolism. Next, the effect of diabetes and obesity on bone was discussed in respect to the decrease in bone quality and increase in the fracture risk of diabetic patients. Factors, which may contribute to these changes, include higher incidence of falling among diabetic patients, and a negative effect of hyperglycemia on bone, which leads to accumulation of collagen cross-links, which change bone biomechanical properties. In addition, structure/function of bone marrow could be altered leading to the changes in bone cell differentiation. Such changes are responsible for bone loss in patients on anti-diabetic therapy with TZDs. Thus, the beneficial effects of TZDs on insulin sensitivity, activation of endocrine properties of fat, and increase in energy metabolism are associated with the negative effects on bone, which include bone loss and increase in bone fracture risk. In summary, *in vitro* and *in vivo* evidence indicate that bone fat is very similar to the extramedullar fat in respect to molecular mechanisms regulating its development and its endocrine function. The endocrine signals generated by bone fat may have either a local effect on bone by regulating a development of osteoblast and osteoclast, or may contribute to the overall endocrine signaling. Moreover, pathophysiologic changes in energy metabolism as well as therapies which modulate energy balance affect bone mass and quality, indicating that bone is a part of energy metabolism system.

In the second presentation “Nutritional hormones and the entero-osseous axis” Dr. Isales discussed the cross-talk between bone and guts mediated by incretin hormones, such as GIP and GLP. These hormones are produced in response to nutrients in the intestine and stimulate insulin production in the pancreas. Interestingly, they also control bone turnover, in response to the nutrient levels, through their receptors which are expressed in bone cells. Dr. Isales also proposed a model according to which bone has a different function in the regulation of energy balance in physiological and

pathophysiological conditions (obesity and diabetes). According to this model, in conditions of limited nutrient availability bone serves as a fuel rod providing ions, hormonal signals and nutrients, as evidenced by the fact that markers of bone breakdown increase during periods of fasting and decrease immediately after eating. These “physiological” changes in bone turnover are therefore primarily regulated by the Brain-Bone-Gut axis with the brain regulating food intake and neural sympathetic output affecting bone mass and with the gut primed to maximize nutrient absorption and their delivery to the bone by the use of gut hormones such as GIP, GLP-2 and insulin. In pathophysiological conditions such as obesity, in the presence of unlimited amounts of nutrients, fat has become a major regulator of bone turnover through release of adipokines/cytokines. Evidence of this fat-bone connection recently became evident when the anti-diabetic class of drugs, the thiazolidinediones (TZDs) which sensitize fat and muscle to insulin, were found to decrease bone mass and increase fracture risk among diabetic patients. Therefore, in these obese-diabetic patients, the “pathophysiological” changes in bone turnover are primarily regulated by the Fat-Bone-Muscle axis.

In the presentation “Reciprocal regulation of bone and energy metabolism”, Dr. Lee discussed a role of bone-derived hormone osteocalcin in regulation of insulin production by pancreas and adiponectin production by fat. This interesting paradigm opens a new possibility that bone is an essential provider of endocrine signaling of energy metabolism.

In the presentation “Common regulatory pathways controlling energy metabolism and bone mass”, Dr. Kawai discussed a role of nocturnin, a protein which is a part of the circadian system, in the regulation of IGF-1 production in bone and liver. Nocturnin acts as a negative regulator of osteoblast differentiation and IGF-1 production. Most interestingly, its expression is under a direct control of PPAR $\gamma$ , a key molecule for energy balance regulation.

At the end of the session, the following aspects were discussed

1. The possible functions of bone fat including its role in the support for hemastopoiesis, clearance of circulating lipids and adipokine production.
2. The relationship between insulin and bone, specifically whether bone is sensitive to insulin in respect to the metabolic processes, such as glucose and fatty acids metabolism. It was also indicated a relative lack of systematic studies in respect to bone and muscle relationship in normal and pathologic (insulin resistance in diabetes) conditions. It was suggested that more research should be devoted to this area of investigation.
3. The possible mechanisms which coordinate entero-osseus signaling between bone, intestines and pancreas, and whether this system is involved in the regulation of metabolic activities of osteocalcin.
4. The role of circadian system in coordination of metabolic communication between different organs.

In conclusion, this session summarized a new area of investigation in musculoskeletal research relating to the function of bone in the endocrine network of regulation of energy balance. As a result of this interesting session, Dr. Lecka-Czernik and Dr. Isales are writing a review entitled “The skeleton’s emerging role as a key nexus in systemic energy balance”.