

## Insulin, osteoblasts, and energy metabolism: why bone counts calories

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*J Clin Invest.* 2014;124(4):1465-1467. <https://doi.org/10.1172/JCI75554>.

### Commentary

Recent studies have demonstrated that insulin stimulates bone cells to produce and activate osteocalcin, an endocrine hormone that increases the efficiency of glucose metabolism through its actions on the pancreas and other peripheral tissues. In this issue of the *JCI*, Wei and colleagues directly explore the contribution of insulin signaling in osteoblasts to the disturbances in whole-body glucose metabolism associated with a high-fat diet. In mice fed a high-fat diet, increased uptake of saturated fatty acids by the osteoblast accelerates the ubiquitination and degradation of the insulin receptor. In this setting, impairments in osteoblast insulin signaling reduce serum levels of undercarboxylated osteocalcin, which in turn exacerbate insulin resistance in muscle and white adipose tissue. These findings underscore the importance of insulin-responsive skeletal cells as components of a newly appreciated endocrine network critical for regulating global energy homeostasis.

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**Recent studies have demonstrated that insulin stimulates bone cells to produce and activate osteocalcin, an endocrine hormone that increases the efficiency of glucose metabolism through its actions on the pancreas and other peripheral tissues. In this issue of the JCI, Wei and colleagues directly explore the contribution of insulin signaling in osteoblasts to the disturbances in whole-body glucose metabolism associated with a high-fat diet. In mice fed a high-fat diet, increased uptake of saturated fatty acids by the osteoblast accelerates the ubiquitination and degradation of the insulin receptor. In this setting, impairments in osteoblast insulin signaling reduce serum levels of undercarboxylated osteocalcin, which in turn exacerbate insulin resistance in muscle and white adipose tissue. These findings underscore the importance of insulin-responsive skeletal cells as components of a newly appreciated endocrine network critical for regulating global energy homeostasis.**

**Conflict of interest:** The authors have declared that no conflict of interest exists.

**Citation for this article:** *J Clin Invest.* 2014; 124(4):1465–1467. doi:10.1172/JCI75554.

### Bone as a metabolic organ: lessons from evolution

The evolution of a large appendicular skeleton powered by robust skeletal muscles in

early tetrapods was a successful strategy for ambulation on land. Additionally, the new skeleton served as a repository for calcium, a scarce commodity in the terrestrial habitat, and the emergence of the parathyroid gland at this juncture provided the means to rapidly access bone calcium through osteoclast-mediated liberation from skeletal stores (1). However, the upgraded musculoskeletal system also increased overall fuel requirements and altered global energy balance, prompting the evolution of other endocrine networks to coordinate energy expenditure (2). Prominent among these emerging networks were the leptin and insulin/insulin-like growth factor pathways, which have assumed central roles in growth and metabolism in higher organisms (3, 4). The importance of these meta-



bolic pathways in modern mammals is illustrated by common metabolic diseases, such as osteoporosis, diabetes, and obesity, caused by genetic or environmental disturbances in endocrine control mechanisms.

In contrast to the large number of studies on energy metabolism in muscle and adipose tissue, surprisingly little attention has been paid to understanding the bioenergetics of bone metabolism. The sheer size of the skeleton alone implies that its energy requirements should have an impact on global metabolic demands, particularly during growth and remodeling. Indeed, mature osteoblasts that are actively synthesizing and mineralizing matrix exhibit abundant mitochondria, consistent with the increased metabolic demand during this active phase of their life span (5). Likewise, osteocytes, which represent terminally differentiated osteoblasts, survive for years embedded in mineralized bone at densities of greater than 10,000 cells per cubic millimeter. These cells are the main source of the phosphate-regulating hormone FGF23 (6) and maintain an extensive lacunar-canalicular network that interconnects bone cells throughout the skeleton.

The first clues that bone might participate in metabolic homeostasis came from studies by Ducy and colleagues, who demonstrated that leptin alters bone mass through a hypothalamic relay (7). Further work led to the recognition that leptin's central effect on the osteoblast also contributes to the hormone's influence on insulin secretion (8). More recently, insulin signaling in the osteoblast was found to be required for proper glycemic control in mice (9, 10). Indeed, disturbances in glucose homeostasis, including glucose intolerance and insulin resistance, in mice specifically lacking *Insr* in osteoblasts could be largely corrected by treatment with bioactive, undercarboxylated osteocalcin (ucOCN); therefore, insulin receptor signaling in osteoblasts increases the production and bioavailability of osteocalcin, which is made exclusively by osteoblasts and osteocytes, and acts in an endocrine fashion to regulate pancreatic insulin secretion and peripheral insulin responsiveness (11, 12). These observations strongly suggest that osteoblasts and osteocytes participate in the normal control of global glucose homeostasis.

### A model of insulin resistance in bone

In the current issue of the *JCI*, Wei and colleagues (13) use both genetic and physiologic approaches to more directly probe

the characteristics of the osteoblast insulin receptor in the context of diet-induced disturbances in metabolism. Mice engineered to modestly overexpress (via the *Col1a1* promoter) or underexpress (via osteoblast-specific *Insr* haploinsufficiency) the insulin receptor in osteoblasts were metabolically normal until challenged with a high-fat diet (HFD). Under these conditions, mice overexpressing the insulin receptor in osteoblasts exhibited better glucose tolerance and were more responsive to insulin than controls, whereas *Insr*-underexpressing mice exhibited more severe glucose intolerance compared with that of control animals. In accordance with previous studies linking insulin-dependent effects on osteocalcin bioavailability to osteoclast-mediated decarboxylation and release from the bone matrix (10), bone resorption and serum ucOCN were reduced in WT mice fed a HFD, while mice with increased or decreased insulin signaling in osteoblasts had greater or lesser amounts of ucOCN, respectively. Importantly, Wei et al. revealed that reduced insulin sensitivity of bone also contributes to the glucose intolerance seen in normal mice fed a HFD.

Remarkably, Wei and colleagues (13) found that osteoblasts from HFD-fed mice exhibit features of insulin resistance that closely resemble those seen in the liver and muscle. These include a reduced ability of insulin to stimulate phosphorylation of IRS1/2, a defect that has been linked to increases in circulating and tissue levels of saturated, lipotoxic fatty acids that raise intracellular diacylglycerol levels (14). To explore the link between lipotoxicity and dysfunctional insulin signaling in bone, Wei et al. treated primary osteoblasts with saturated fatty acids and confirmed an inhibitory effect on insulin receptor signaling. Intriguingly, stearate in particular caused a reduction in insulin receptor abundance due to increased SMURF-dependent ubiquitination, suggesting a unique pathway for the development of insulin resistance in bone.

### Implications and perspectives

The studies by Wei et al. (13) strengthen the case for a link between bone and energy glucose metabolism, in which the insulin receptor and osteocalcin are central components. Wei and colleagues favor a mechanism involving insulin's ability to increase the bioavailability of the undercarboxylated form of osteocalcin, which in turn facilitates uptake and metabolism of glucose by

adipose and muscle; however, the mechanism whereby ucOCN facilitates glucose uptake by muscle and adipose is unclear. A putative receptor for ucOCN, GPCR6A, has been identified and implicated as the mediator of ucOCN action on the pancreas and testicular Leydig cells (15), though it remains to be determined whether this same receptor mediates other insulin-sensitizing actions. Indeed, recent examination of central actions of osteocalcin suggests the existence of another receptor, which apparently mediates certain behavioral actions of osteocalcin (16).

As acknowledged by Wei et al., it seems highly likely that insulin signaling in osteoblasts also affects global glucose homeostasis though osteocalcin-independent mechanisms. For example, insulin is known to stimulate glucose uptake by osteoblasts (17), which express several high-affinity insulin-responsive glucose transporters (18); therefore, any loss of insulin-dependent glucose uptake by osteoblasts (e.g., high-fat intake) could have a profound affect on whole-body glucose disposal and contribute to the disturbances in glucose homeostasis. Studies to precisely define the relative contribution of bone cells to whole-body glucose disposal will require more rigorous approaches, such as the use of euglycemic clamps. Finally, very recent studies show that the ability of WNT/LRP5 signaling to promote osteoblast differentiation depends in part on the ability of osteoblasts to activate key glycolytic enzymes that promote aerobic glycolysis (19). Such data indicate that factors other than insulin play a role in the regulation glucose utilization by osteoblasts.

In summary, the studies by Wei et al. (13) add to a growing body of data that implicate bone and its cells as an important metabolic organ that is functionally linked to other metabolically active tissues by common endocrine hormones, such as insulin. Future studies are needed to more precisely define the fraction of the whole-body caloric intake that is required for bone cells to function relative to that required by other tissues. In addition, it would seem important to know what types of fuels are used by osteoblasts and whether fuel preferences vary according to different functional demands of osteoblasts at different stages of their life cycle. From a clinical perspective, studies investigating the possibility that metabolic disturbances underlying the pathogenesis of diabetes and obesity might also affect the skeleton and vice versa are



already underway. Answers to such questions will certainly expand our understanding of the biology of the skeleton and might ultimately aid in the diagnosis and management of patients with a broad range of metabolic diseases.

### Acknowledgments

R.C. Riddle is supported by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases of the NIH (DK099134) and a Career Development Award from the Veterans Administration. T.L. Clemens is supported by a Merit Review grant (BX001234) and is the recipient of a Research Career Scientist Award from the Veterans Administration.

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