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

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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 reduces serum levels of undercarboxylated osteocalcin, which in turn

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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* haplinsufficiency) 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) 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 relatively 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.

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