Osteocalcin: a pivotal mediator or an innocent bystander in energy metabolism?

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Introduction

The importance of the bone–kidney axis in physiologic regulation of mineral ion homeostasis has been extensively studied and documented. Numerous research studies have convincingly shown that pathology in one organ can affect the functionality of the other organ. For instance, chronic kidney disease (CKD) patients usually present with complications of bone anomalies that vary from fractures (due to increased bone fragility) to extraskeletal calcification (due to mineral ion dysregulation). These skeletal anomalies in CKD–mineral bone disorder (CKD–MBD) are partly related to decreased osteoblastic differentiation that impairs the anabolic responses of the bone [1]. CKD patients in their forties who are undergoing dialysis treatment are 80 times more likely to acquire hip fractures than age- and sex-matched controls [2]. Furthermore, studies have documented a linear correlation between insulin resistance and the decline of renal functions [3]. In a large cohort of >6000 non-diabetic individuals, insulin resistance and concomitant hyperinsulinemia were detected in CKD patients [4]. Why CKD patients are more likely to develop insulin resistance is not yet clear, and carefully designed studies are needed to determine whether impaired osteoblastic activity in CKD may induce such resistance. Such possibilities arise from the recent discoveries that have shown that osteoblast-derived factor can affect energy metabolism by influencing insulin secretion [5,6].

Osteoblasts

The bone is a delicate structure containing various types of mesenchymal-originated cells, including osteoblasts, chondrocytes, bone marrow stromal cells and adipocytes [7]. Osteoblasts are responsive to a wide range of factors during the differentiation process from mesenchymal stem cells, which include, but are not limited to, fibroblast growth factors (FGFs), bone morphogenic proteins (BMPs), RUNX2 and Osterix [8–10]. Osteoblasts are indispensable cells for bone growth, development and maintenance, and by producing the required amount of matrix proteins, these cells help to maintain normal homeostatic balance of the bone. As it happens, bone constitutes the largest mineralized connective tissue mass in the body.

Recent studies have identified important roles of bone-derived factors in regulating functions of various tissues and organs, including kidney, parathyroid gland, adipose tissues, muscles and pancreas. For instance, bone-derived FGF23 is a master regulator of renal phosphate metabolism [11,12], whereas the bone–parathyroid gland axis is involved in regulating calcium balance [13–15]. Similarly, osteoimmunology is an emerging field of research [16], while bone provides a microenvironment for rapid growth of metastatic tumor cells [17]. A bone–adipocyte interaction is believed to exert a bimodal response to bone formation. A moderate increase of adipocyte-derived hormone leptin can stimulate bone formation, whereas higher levels have been shown to inhibit it [18,19].

Bone remodeling is a complex process, and vitamin D, parathyroid hormone (PTH) and reproductive hormones are traditionally thought to be involved in such remodeling. However, recent studies have uncovered the role of insulin as an additional factor involved in the skeletal remodeling process. Studies have further shown that osteoblastic insulin signaling is important for glucose metabolism [5,6]. Of particular importance are the insulin receptors present in the osteoblasts and the finding that insulin, through interacting with the cell surface receptors, releases osteocalcin to influence systemic glucose homeostasis [5,6].

Osteocalcin

Osteocalcin is a non-collagenous, vitamin K-dependent protein produced by osteoblasts. The osteocalcin protein contains three residues of the amino acid gamma-carboxyglutamic acid (Gla). The Gla residues, in the presence of calcium, facilitate its binding to hydroxyapatite and eventual deposition in the mineralized bone matrix. Serum
Osteoblast and insulin signaling

Insulin signaling and osteocalcin

Insulin signaling is one of the most well-dissected pathways in both mammalian and non-mammalian systems. Experimental studies have reported that insulin signaling in osteoblasts is not only important for normal bone acquisition but also stimulates osteocalcin production. Molecular analysis suggests that insulin signaling facilitates bone formation by suppressing Twist2 (Runx2 inhibitor), a protein that inhibits osteoblast development and thereby enhances expression of osteocalcin. Additional studies are needed to determine whether bioactive osteocalcin can alter osteoblast number and function. A mouse genetic study found increased bone mass without impaired bone resorption in osteocalcin-deficient mice.

The acidic conditions (low pH) created by the osteoclastic resorption process are thought to activate osteocalcin inside the bone, which is then released from the bone to stimulate pancreatic insulin secretion (Figure 1). Along similar lines of observation, mice lacking insulin receptors in osteoblasts develop peripheral insulin resistance, whereas osteocalcin infusion can improve insulin sensitivity in insulin receptor mutant mice. Because osteoclastic bone resorption is anticipated to influence bioactivity of osteocalcin, it will be interesting to determine whether treated inhibitors of bone resorption (bisphosphonates) can induce glucose intolerance in osteoporotic patients. Similarly, estrogen has suppressive effects on osteocalcin, and it will be clinically interesting to know whether estrogen treatment can induce insulin resistance and obesity. Another important area that needs further research is the clinical associations among vitamin K status, osteocalcin and insulin responses. In a recent study, higher phylloquinone (vitamin K1) intake has been shown to be associated with greater insulin sensitivity and glycemic status in ~2000 studied subjects in the Framingham Offspring cohort. In a similar line of study on elderly individuals, a daily supplementation of 500 μg of phylloquinone for 36 months has shown a protective effect on the progression of insulin resistance in older men. Of relevance, elderly men receiving vitamin K supplementation had less plasma undercarboxylated osteocalcin compared with the control group.

Osteocalcin and osteorenal diseases

Serum osteocalcin levels are high in patients with CKD. The increased serum accumulation of osteocalcin in patients with CKD can be related to decreased renal clearance, increased bone metabolism, or a combination of both. Delmas et al. concluded that for normal subjects and patients with mild-to-moderate renal impairment, elevated
undergoing dialysis treatment are related to vascular calcification [33]. Of particular interest, undercarboxylated osteocalcin levels have the potential to reflect the status of insulin sensitivity by affecting osteocalcin production and its bioactivities. Of clinical significance, long-term use of warfarin has been shown to be associated with aortic valve calcification in hemodialysis patients [42]. Irrespective of disease pathology, circulatory levels of osteocalcin reflect increased bone turnover rather than decreased renal filtration. In patients with CKD, the progressive increase in serum osteocalcin levels closely corresponded with intact PTH and alkaline phosphatase levels. More importantly, such increases in serum osteocalcin levels reflect the severity of the bone lesions [30]. In cadaveric allograft kidney recipients, significant increases in serum osteocalcin levels were detected at 3 and 6 months after transplantation. Such increases in levels of osteocalcin also significantly correlated with serum alkaline phosphatase levels, implicating an increase in osteoelastic activity following renal transplant [31]. It is not yet clear why the increased osteocalcin level is unable to prevent insulin resistance in CKD patients. Determining the bioactivity of osteocalcin in these patients will be an important step towards understanding its role, if any, in disease progression. A recently developed triple enzyme-linked immunosorbent assay system for quantification of total carboxylated and uncarrboxylated osteocalcin may provide a viable tool to determine the hormonal activity of osteocalcin in experimental set-up [32].

The progression of vascular calcification has similarities to bone formation, and the serum undercarboxylated osteocalcin levels are higher in patients with carotid artery calcification [33]. The investigators believe that circulating undercarboxylated osteocalcin levels have the potential to be a biomarker of vascular calcification [33]. Of particular importance, 50% of mortalities in patients with CKD undergoing dialysis treatment are related to vascular calcification [34–36]. In an in vitro study using bovine aortic smooth muscle cell, exogenous osteocalcin has been shown to inhibit the calcification process [37]. In an experimental aortic calcification model induced by oversize balloon angioplasty in rabbits, the calcified foci were noted by 2 days post-injury, while osteocalcin was detected on Day 14 post-injury, suggesting that osteocalcin may not be involved in the initial events of calcification [38]. Carefully designed studies are required to assess the contribution of calcifying vascular smooth muscle cells to overall osteocalcin levels and determine whether such osteocalcin can play a role in the genesis of insulin resistance commonly observed in CKD patients. As osteocalcin can be generated by calcifying vascular smooth muscle cells and because vascular calcification has been associated with insulin resistance, studies focusing on determining the bioactive status of osteocalcin may explain discrepancies between human observations and mouse studies [5,6].

Experimental studies have shown that undercarboxylated osteocalcin can regulate insulin and adiponectin secretion, and in accord with the animal studies, a positive association between osteocalcin and adiponectin was detected in CKD patients [39]. Despite increased levels of osteocalcin in CKD patients, why these patients are more likely to develop insulin resistance is an important question that needs to be settled in clinical trials. In a separate study, undercarboxylated osteocalcin levels negatively correlated with fat mass, fasting plasma glucose and HbA1c levels in male type 2 diabetic patients. Such correlation was independent of age, duration of diabetes, body stature, renal functions, and glucose or fat metabolism [40]. Further studies are necessary to determine how undercarboxylated osteocalcin interacts with beta cells of the pancreas and whether there are osteocalcin-specific cell surface receptors involved. Identification of an osteocalcin-specific cell surface receptor and its affinities for various forms of osteocalcin is necessary to gain further insights into its molecular regulation. The production of osteocalcin by human adipose tissue adds additional complexity in energy metabolism [41]. Foresta et al. not only found a lower undercarboxylated osteocalcin in the overweight and obese patients but also detected expression of osteocalcin mRNA in subcutaneous and omental adipose tissues [41].

Conclusion

Despite extensive molecular, genetic and biochemical studies on osteocalcin biology, we have a very limited understanding of the diverse functions of this unique molecule and its clinical utility as a therapeutic target. As mentioned, osteocalcin is a vitamin K-dependent protein. The circulating undercarboxylated osteocalcin is increased in vitamin K deficiency and therefore used as a clinical biomarker of vitamin K status in patients. It will be important to know whether warfarin treatment (a vitamin K antagonist) can influence insulin sensitivity by affecting osteocalcin production and its bioactivities. Of clinical significance, long-term use of warfarin has been shown to be associated with aortic valve calcification in hemodialysis patients [42]. Irrespective of disease pathology, circulatory osteocalcin levels also reflect osteoelastic activities in various human diseases, including CKD–MBD. It is necessary to mention that despite the utility of osteocalcin and bone-specific alkaline phosphatase as bone-forming markers, these molecules are unable to offer additional information to determine the underlying histologic variants of skeletal diseases.

Experimental animal studies have found that Esp-null mice with increased levels of undercarboxylated osteocalcin are protected from diet-induced obesity and diabetes [17], whereas infusion of undercarboxylated osteocalcin in the insulin receptor mutant mice improved such metabolic abnormalities, including insulin resistance [5]. If mouse studies are to implicate human responses, the ratio of undercarboxylated osteocalcin and total osteocalcin may reflect the status of insulin sensitivity. Furthermore, it will be important to know whether therapeutic maneuvering of bone function may become a strategy to treat patients suffering from metabolic diseases due to altered glucose and lipid homeostasis. From the renal medicine perspective, fine-tuning the effects of clinical therapy to decrease insulin resistance in patients with CKD and reduce the disease burden is desirable. Whether manipulating osteocalcin bioactivities can assist in achieving such a desirable outcome is unknown but worth investigating. Perhaps the most fascinating prospect is the use of osteocalcin as a therapeutic tool to promote insulin secretion in diabetic individuals to reduce glucose burden and minimize associated complications, including diabetic nephropathy. However, before designing any therapeutic strategies, further human studies are necessary to clarify whether osteocalcin is a pivotal mediator or an innocent bystander in energy metabolism.
References


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