

## Osteocalcin Possesses Hormonal Function Linking Bone to Glucose Metabolism

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The number of patients with diabetes mellitus and osteoporosis is rapidly increasing in industrialized countries where Western-style aging societies are prevalent. Although the incidence of osteoporosis and type 2 diabetes mellitus is known to increase in prevalence with aging, both diseases were traditionally viewed as separate entities. However, the relationship between diabetes and osteoporotic fractures is recently and increasingly becoming recognized.

Osteocalcin, one of the osteoblast-specific proteins, has several hormonal features and is secreted in the general circulation from osteoblastic cells. Ducy and Karsenty's group previously generated *Osteocalcin* knockout mice to examine the role of osteocalcin in bone. While analyzing these mutant mice, they surprisingly found an abnormal accumulation of visceral fat. They then conducted experiments with employing the mice and showed that osteocalcin increased the expression of insulin in pancreatic  $\beta$  cells as well as of adiponectin in adipocytes [1]. *Osteocalcin* knockout mice displayed hyperglycemia and glucose intolerance. In addition, they found that  $\beta$ -cell proliferation and insulin secretion were decreased, and that insulin resistance by the inhibition of adiponectin expression as well as the accumulation of fat mass was observed in the mice. This is the first evidence suggesting that feedback loops exist among bone, pancreas and adipose tissue.

Since this exciting evidence was reported, of particular interest is whether osteocalcin level in the circulation is associated with glucose metabolism in humans. We previously reported that serum osteocalcin was inversely associated with glucose and visceral fat mass and positively with serum adiponectin level, parameters of insulin secretion and its sensitivity in patients with type 2 diabetes [2,3]. Kindblom et al. showed that osteocalcin level was inversely related to plasma glucose level and fat mass in elderly non-diabetic persons [4]. Fernandez-Real et al. reported that serum osteocalcin level was associated with insulin sensitivity in non-diabetes subjects [5]. Pittas et al. demonstrated that serum osteocalcin concentration was inversely associated with fasting plasma glucose, fasting insulin, a parameter of insulin resistance, and body fat in cross-sectional analyses. They also found that osteocalcin level was associated with change in fasting plasma glucose in prospective analyses [6]. In addition, we most recently reported a longitudinal study showing that change in osteocalcin was negatively correlated with change in HbA1c during treatments of type 2 diabetes [7]. These experimental and clinical findings suggest that bone metabolism and glucose/fat metabolism are associated with each other through the action of osteocalcin.

Osteocalcin has 49 amino acids and undergoes  $\gamma$ -carboxylation of glutamyl residues at positions 17, 21 and 24, which facilitates binding of osteocalcin to hydroxyapatite in bone. Because carboxylated osteocalcin has a higher affinity for hydroxyapatite than uncarboxylated one, a question was raised whether the level of  $\gamma$ -carboxylation of osteocalcin could affect the function of osteocalcin. Karsenty's group reported that mice deficient of *ESP*, a model of gain of osteocalcin bioactivity, displayed increased ratio of uncarboxylated osteocalcin to total osteocalcin in sera [1]. In addition, they confirmed that recombinant uncarboxylated osteocalcin administration regulated gene expression

in  $\beta$  cells and adipocytes (including adiponectin expression), and affected the development of metabolic diseases, obesity, and type 2 diabetes in wild-type mice [8]. In clinical studies, we and others found that uncarboxylated osteocalcin was associated with glucose level and insulin secretion as well as visceral fat accumulation [9,10]. However, it is still unclear how uncarboxylated osteocalcin affects the expression of adiponectin and insulin or why carboxylated one is not able to affect glucose homeostasis.

Recently, two independent groups reported that insulin receptor signaling in osteoblasts regulated peripheral adiposity and glucose metabolism [11,12]. They found that deletion of insulin receptor in osteoblast showed decreases in osteoblast development and osteocalcin expression as well as increases in blood glucose level and insulin resistance. Their results indicate the existence of a bone-pancreas endocrine loop through which insulin signaling in the osteoblast ensures osteoblast differentiation and stimulates osteocalcin production, which in turn regulates insulin sensitivity and pancreatic insulin secretion.

It has been shown that adipose tissue regulates bone metabolism. Leptin derived from adipocytes is reported to regulate bone mass accrual and appetite by inhibiting serotonin synthesis and/or release by brainstem neurons [13]. Because the regulation of these two functions by leptin goes in the same direction, leptin does coordinate bone remodeling with energy metabolism. On the other hand, we have shown that osteoblast has an adiponectin receptor and the adiponectin signaling stimulates the differentiation of osteoblasts and osteocalcin expression [14]. Since adiponectin is involved in osteoblastogenesis as well as osteocalcin expression and osteocalcin alternatively stimulates the expression of adiponectin in adipocytes, it is hypothesized that endocrine loop might exist between bone and adipose tissue.

Serum osteocalcin and adiponectin levels are known to be different between men and women. This suggests that there might be difference in the effect of osteocalcin on glucose metabolism between them. Indeed, serum osteocalcin is correlated with serum adiponectin level in women, but not men [2,3]. Although it is reported that serum osteocalcin was associated with glucose level in both sexes, we found that low serum osteocalcin was more likely related to oral glucose tolerance test-induced hyperglycemia and hyperinsulinemia in women than in men [3]. It is necessary to clarify whether or not there is a

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Received April 28, 2011; Accepted April 30, 2011; Published May 04, 2011

**Citation:** Kanazawa I (2011) Osteocalcin Possesses Hormonal Function Linking Bone to Glucose Metabolism. J Diabetes Metab 2:105e. doi:10.4172/2155-6156.1000105e

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gender difference in the effect of osteocalcin on glucose metabolism as well as the incidence of obesity and type 2 diabetes.

Several studies have shown that osteoporosis is associated with cardiovascular disease and influences mortality. Mortality is increased following several types of osteoporotic fractures, and an association between low bone mineral density and mortality, especially due to cardiovascular diseases, has been described [15]. Accumulating evidence indicates that similar pathophysiological mechanisms lead to the progression of atherosclerosis [16]. Moreover, it is reported that osteocalcin-positive mononuclear cells were associated with the severity of aortic calcification [17]. Because osteocalcin regulates glucose and energy homeostasis, it is assumed that there is a relationship between serum osteocalcin and atherosclerosis parameters. In a clinical study, we found that serum osteocalcin was significantly and inversely correlated with atherosclerosis parameters [2]. Moreover, our longitudinal study also indicated that low serum osteocalcin level was associated with the deterioration of atherosclerosis independently of other atherosclerosis-related risk factors in patients with type 2 diabetes [7]. Pennisi et al. demonstrated that postmenopausal women with carotid atherosclerosis had lower level of osteocalcin than healthy controls [18]. Zhang et al. showed that serum osteocalcin level was significantly lower in the coronary heart disease (CHD) group than in the non-CHD group and was significantly decreased with the increasing of number of diseased vessels [19]. However, it is unclear how osteocalcin affects atherosclerosis and whether osteocalcin predicts the incidence of cardiovascular diseases.

Recently, Karsenty's group showed that insulin signaling in osteoblast induced activation of osteoclasts via inhibiting osteoprotegerin expression with decarboxylation of osteocalcin occurring in resorption lacunar, resulting in an increase in uncarboxylated osteocalcin level [12]. Because they found that insulin signaling in osteoblasts did not affect osteocalcin activity or glucose metabolism when bone resorption was blocked, osteoclast activity is also important for regulating glucose metabolism by osteocalcin.

Vitamin K promotes  $\gamma$ -carboxylation of osteocalcin, leading to decrease uncarboxylated osteocalcin. This suggests that vitamin K supplementation and medication of vitamin K might have a negative impact on glucose homeostasis. However, several studies showed that higher intake of vitamin K were related to better insulin sensitivity and lower prevalence of hyperglycemia [20,21]. These findings are inconsistent with previous studies showing that uncarboxylated osteocalcin increased insulin sensitivity and decreased blood glucose. On the contrary, warfarin, an anticoagulant in common clinical usage, antagonizes vitamin K-dependent  $\gamma$ -carboxylation of osteocalcin. There are no studies examining whether warfarin is able to improve insulin resistance and glycemic control by stimulating the uncarboxylated osteocalcin production. In addition, drugs for osteoporosis such as estrogen and bisphosphonate also affect serum uncarboxylated osteocalcin level by inhibiting bone resorption. These agents might influence glucose metabolism and the incidence of type 2 diabetes.

### Future directions to understand the hormonal function of osteocalcin

Further studies are necessary to find the mechanism how osteocalcin affects pancreatic  $\beta$  cells and adipocytes (a receptor of osteocalcin, its signal transduction etc.) and to clarify whether or not endocrine loop exists between bone and adipose tissue.

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- Longitudinal studies will clarify whether osteocalcin level predicts incidence of type 2 diabetes or cardiovascular events.
- Large scale cross-sectional studies and longitudinal studies will be conducted to compare whether associations of undercarboxylated osteocalcin with specific outcomes are stronger than those of total or carboxylated osteocalcin.
- Studies will be conducted to examine whether there is a gender difference in the effect of osteocalcin on glucose metabolism.
- Osteoclast-mediated decarboxylation of osteocalcin will be focused in humans.
- Effects of drugs affecting  $\gamma$ -carboxylation of osteocalcin such as vitamin K and warfarin on blood glucose level will be evaluated. Also, it will be examined whether the drugs for osteoporosis influence glucose metabolism.

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