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Dose Adiponectin Have Adverse Effects on Bone Mass and Fracture?

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Previous studies on adipocyte function have revealed that adipose tissue is not only an energy-storing organ, but also a secretor of a variety of biologically active molecules named adipocytokines. Since adipocytokines were discovered, tons of investigators have been examining their role in metabolic homeostasis and diseases. Adiponectin, one of the adipocytokines, has recently attracted widespread attention, especially in the diabetes field, due to its beneficial anti-diabetic and anti-atherosclerotic effects in the regulation of energy homeostasis and insulin sensitivity [1]. In addition, it has been shown that adiponectin function is involved in the pathologies of cancer and rheumatoid arthritis [1]. Because of its numerous beneficial biological functions, it is suggested that adiponectin administration is a potential therapeutic agent and that treatments increasing blood adiponectin levels and stimulating adiponectin action benefits healthy problems.

Bone is continually remodeled according to physiological circumstances through bone formation by osteoblasts and bone resorption by osteoclasts, and bone mass and turnover are maintained by their coordinated balance in healthy adults. Many systemic and local factors such as insulin-like growth factor-I and bone morphogenetic proteins are known to be involved in the regulation. A number of basic and clinical studies investigating the effects of adiponectin on bone metabolism as well as its association with bone mineral density (BMD) and the risk of fracture have been reported. However, these studies suggest that adiponectin may have adverse effects on bone mass and fracture risks.

Adiponectin and its receptor are expressed in osteoblasts [2-4]. Adiponectin stimulates cell growth and differentiation of osteoblastic cells [2-4]. In addition, blockage of adiponectin signal by siRNA of adiponectin receptor showed decreased alkaline phosphatase activity and expression of differentiation markers, type I collagen and osteocalcin, as well as impaired mineralization in osteoblastic cells [4]. Although adiponectin is reported to inhibit murine osteoclast activity [5], Luo et al. revealed that human osteoclastic cells had no expression of adiponectin receptors and adiponectin administration showed no effects on osteoclast activity in the cells [6]. In contrast, adiponectin indirectly activated osteoclasts through stimulation of receptor activator for nuclear factor B ligand (RANKL) expression and inhibition of osteoprotegerin (OPG) expression in osteoblasts. Taken together, these *in vitro* findings suggest that adiponectin stimulates osteoblast activity and accelerates bone turnover through RANKL/OPG expression.

In consistent with studies using cell culture experiments, a number of clinical studies showed that adiponectin levels in circulation were associated negatively with BMD and positively with bone turnover markers [7,8]. In addition, we previously demonstrated that serum adiponectin levels were positively associated with the presence of vertebral fractures in men with type 2 diabetes [8]. Other two groups also reported that higher serum adiponectin levels were associated with increased fracture risks in male subjects [9,10]. Recently, a meta-analysis investigating the association of adipocytokines such as adiponectin and leptin with BMD and fracture risk was reported. Adiponectin is the most relevant adipocytokine negatively associated

with BMD independent of gender and menopausal status [11] In the analysis, high levels of adiponectin were associated with an increased risk of vertebral fractures only in men. These clinical reports and meta-analysis suggest that adiponectin is a negative factor for BMD and bone strength especially in men. However, there is another possible explanation that serum adiponectin levels in subjects with osteoporosis reactively elevate through up-regulated synthesis and secretion to protect bone from osteopenia, namely a compensate response of adiponectin expression for bone loss. This hypothesis is supported by the evidence that the serum OPG level also correlates negatively with BMD, although it acts as a decoy receptor for RANKL and protects bone from osteopenia through inhibiting osteoclastic activities [12]. Thus, further large-scale longitudinal studies focusing on the association between adiponectin, BMD loss, and fracture risk are necessary in future.

However, several *in vivo* studies using overexpression and knockout models of adiponectin have assessed the role of adiponectin in bone, but the results have been conflicting [5,13-15]. Ohshima et al. and Mitsui et al. demonstrated that overexpression of adiponectin in the liver enhanced bone formation and showed a gain of bone mass compared with wild-type mice [5,13]. In contrast, Ealey et al. reported that adiponectin-overexpressing mice had a significantly lower bone mass and that the peak load of femur neck and vertebra was significantly lower than WT mice [14]. Shinoda et al. showed no significant differences in bone mass or turnover in adiponectin-overexpressing mice in the liver or in adiponectin knockout mice compared with their littermates [15]. Adiponectin is known to enhance insulin activity while reducing insulin resistance. Most studies have consistently shown that adiponectin knockout mice have either spontaneous or diet-induced insulin resistance with hyperinsulinemia [16], which affects bone metabolism and causes an increase in bone mass. Adiponectin also plays important roles in the liver, muscle, pancreas, and hypothalamus, which might affect bone metabolism. In addition, because adiponectin receptors are ubiquitously expressed in various tissues, adiponectin may have both direct and indirect effects on bone. Therefore, regarding the conflict results of these *in vivo* studies, physiological compensation and adaptation might contribute to the complexity of the *in vivo* role of adiponectin in bone metabolism. To further understand the role of adiponectin in bone, bone-specific adiponectin overexpression and adiponectin receptor knockout models might be useful.

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On the other hand, osteocalcin, an osteoblast-specific secreted protein, has been shown to increase the expression of insulin in pancreatic β cells as well as the adiponectin in adipocytes [17]. These findings suggest that body fat and bone mass are associated with each other. Indeed, in clinical studies, we and others have demonstrated that serum osteocalcin levels are associated negatively with plasma glucose levels and fat mass, and positively with serum adiponectin levels [18-20]. Recently, two independent groups showed that insulin receptor signaling in osteoblasts controlled osteoblast development and osteocalcin expression and regulated peripheral adiposity and glucose metabolism [21,22], indicating 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. Since the previous studies described above have shown that adiponectin is involved in osteoblastogenesis and bone turnover and that osteocalcin stimulates the expression of adiponectin in adipocytes, it is rational to hypothesize that an endocrine loop modulated by the activity of adiponectin and osteocalcin exists between bone and adipose tissue. In addition, adiponectin is reported to enhance the action of insulin on osteoblast differentiation [15]. Therefore, adiponectin might play a role in part of the endocrine loop between bone, pancreas, and adipose tissue. However, there is no direct evidence up to date. Further studies are thus necessary to examine the role of adiponectin in the endocrine loop between bone and adipose tissue.

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