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BONE AND DIABETES (A SCHWARTZ AND P VESTERGAARD, SECTION EDITORS)

Osteoglycin and Bone—a Systematic Review

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Abstract

Purpose of Review Bone turnover is a regulated process. Osteoglycin is suggested to have an important impact on bone function but may also affect cardiovascular and metabolic functions. This review investigates the action of osteoglycin in bone as well as its potential endocrine effects.

Recent Findings Osteoglycin is expressed by several tissues including bone and muscle. Some studies suggest that osteoglycin increases osteoblast differentiation whereas others suggest that osteoglycin decreases osteoblast differentiation. Thus, findings on the influence of osteoglycin in bone are conflicting. A recent study found increased bone mass in osteoglycin deficient mice. Another study reported that osteoglycin is a marker of low bone mineral density and vertebral fractures in women with type 2 diabetes. Furthermore, clinical studies link osteoglycin to insulin resistance and cardiovascular disease.

Summary Osteoglycin may be a novel marker of a muscle, pancreatic, and bone axis. However, current evidence is limited and further research investigating osteoglycin in both a pre-clinical and a clinical setting is needed.

Keywords Bone · Osteoglycin · Insulin resistance · Bone turnover

Introduction

Bone is traditionally regarded as an organ without endocrine activity that provides structure and mechanical strength. Recently, it has been suggested that bone itself could produce proteins with endocrine actions. Osteocalcin is hypothesized to influence muscle insulin resistance and pancreatic release of insulin. Current clinical results on osteocalcin are not in favor of an endocrine action [1]; however, osteoglycin may act as a mediator of a bone, muscle, and pancreatic axis. Osteoglycin is a member of the small leucine-rich proteoglycan family, a distinct group of extracellular proteoglycans that are expressed in bone among other tissues [2]. Osteoglycin is suggested to influence bone turnover and bone function, but may also affect cardiovascular and metabolic functions. This review investigates the action of osteoglycin in bone as well as potential endocrine actions of osteoglycin.

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Methodology

The PRISMA guidelines were followed [3]. A systematic literature search was performed in the database Medline at Pubmed using the search terms “osteoglycin and bone” and “mimecan and bone.” “Mimecan” was included as an earlier term for osteoglycin. The references from other literature reviews were also included in the search. Records on bone structure, bone function, and endocrine action in relation to osteoglycin were selected for this review. All records were included independent of the language of the record, age of the record, or material investigated (human, animal, and cell). The literature search was initially performed on November 16, 2018, and updated on January 29, 2019. In total, 52 unique records were defined and 24 records were included in the systematic literature review.

Bone Composition and Regulation

Bone consists of a mineralized matrix, a non-mineralized matrix (collagen), osteoclasts, osteoblasts, and osteocytes. Bone elicits mechanical resistance from hydroxyapatite crystals and the collagen structure. The network of collagen, primarily type I collagen, provides stability and elasticity [4]. Bone turnover is a coupled process of bone resorption and bone formation [5–8]. Osteoclasts perform the bone resorption by adhering to the underlying bone and secreting acidic proteases that degrade bone [9, 10]. Osteoblasts are derived from mesenchymal stem cells. They perform the bone formation by migrating to the resorption site and creating a non-mineralized matrix (by producing collagen type I and other non-collagenous proteins), and by regulating the following mineralization [11]. Osteocytes are thought to be encased osteoblasts in the mineralized bone that function as sensors of mechanical loading and thus regulate both bone formation and bone resorption [12]. Bone resorption and formation are tightly regulated by parathyroid hormone (PTH), receptor activator of nuclear factor-kappa beta ligand (RANKL), osteoprotegerin (OPG), and sclerostin. PTH increases bone resorption by an osteoclast-mediated mechanism and activates vitamin D in the kidneys [13]. The active 1,25 vitamin D stimulates differentiation of osteoclasts and regulates the mineralization of bone [13]. RANKL is produced by the osteoblasts and promotes differentiation, activation, and survival of osteoclasts [14]. Both PTH and 1,25 vitamin D increase the production of RANKL. Similarly to RANKL, OPG is produced by osteoblasts and is a decoy receptor to RANKL that inhibits the activation of osteoclasts [14, 15]. Sclerostin is an inhibitor of the Wnts, which are small proteins that stimulate osteoblast differentiation and promote bone formation [16].

Osteoglycin and Bone

Osteoglycin was first identified in bovine bone and thought to promote bone formation [17]. Osteoglycin is monogenic expressed by several tissues such as bone, cartilage, cornea, and aorta in bovine [18]. Based on tissue samples from dogs, osteoglycin is expressed in bone tissue and cartilage, whereas it is not expressed in the mitral valve or myocardium [19]. Samples from muscle tissue were not examined in these studies [18, 19]. Osteoglycin is also expressed in human mesenchymal progenitor cells, in which osteoglycin expression increased following exposure to Osterix [20]. The effects of osteoglycin on bone turnover are conflicting based on current evidence. In murine osteoblastic cells, a stable over-expression of osteoglycin decreases the levels of RUNX2 and Osterix mRNA significantly. RUNX2 and Osterix are important promoters of mesenchymal osteoblastic differentiation and maturation of bone, and so, osteoglycin could impair recruitment of bone-forming cells [21, 22]. Nevertheless, stable over-expression of osteoglycin also increases the levels of alkaline phosphatase and osteocalcin mRNA and enhances mineralization, thus pointing towards the activation of mature osteoblasts [23]. Osteocalcin and alkaline phosphatase are products released by osteoblasts and are indices of bone formation but also of osteoblastic differentiation [24]. Similarly, in osteoblastic cell lines, a reduction in endogenous osteoglycin levels show opposite effects compared to osteoglycin over-expression [23]. These results are in contrast to results from bone marrow mesenchymal stem cells derived from a senile mouse model, where in vitro osteoglycin infected lentivirus forces an over-expression of osteoglycin. This over-expression of osteoglycin increases the expression of bone formation pathways like Wnts and RUNX2 and also increases levels of alkaline phosphatase and osteocalcin mRNA, thus promoting osteoblastic differentiation and activity [25•]. Osteoblastic cells present high levels of alkaline phosphatase when exposed to a conditioned medium from the myoblastic cells that over-express osteoglycin [26]. Bone is regulated by mechanical loading since sclerostin decreases by mechanical loading [27]. The expression of osteoglycin in pre-osteoblasts does not seem to be affected by mechanical loading. Low-magnitude and high-frequency mechanical loading does not alter osteoglycin expression in pre-osteoblasts while RUNX2 and alkaline phosphatase increase during the mechanical loading [28]. During use of a random positioning machine that decreases bone formation markers and osteoglycin, low-magnitude and high-frequency mechanical loading abolishes the decrease in osteoglycin [28]. Besides being involved in osteoblastic differentiation, osteoglycin may also be an important factor in collagen maturation and function. Osteoglycin decreases the rate of collagen type 1 fibrillogenesis in vitro [29]. In osteoglycin deficient mice, collagen fibrillogens are abnormal and increased in size compared to wild type mice [30]. It is not known whether this abnormal collagen is dysfunctional. Two studies report on osteoglycin deficient mice. Osteoglycin deficient mice, based on genetic knockout, do not elicit defects in bone structure and appear otherwise normal beside collagen abnormalities [30]. Osteoglycin deficient mice, using CRISPR technology, display significant increases in femoral bone mineral density and bone mineral content as well as femur length compared to wild type mice. Furthermore, bone histomorphometry displays an increased bone mass in osteoglycin deficient mice, which were related to an increase in osteoblast activity, an increase in mineralization, and a decrease in osteoclast number [31••]. While the study from Tasheva and colleagues [30] reports no improvement in bone with x-ray assessment, Lee and colleagues [31••], by using more refined techniques, demonstrate an increase in bone mass in osteoglycin deficient mice primarily due to an increase in osteoblast activity and bone formation compared to bone resorption. The study by Lee and colleagues [31••] suggests that osteoglycin is a

negative regulator of osteoblast activity; nevertheless, evidence is conflicting. Few human studies investigating osteoglycin are present, and only a single study reports on bone-related outcomes. In postmenopausal women with type 2 diabetes, osteoglycin levels are associated with decreased bone mineral density and the presence of vertebral fractures [32••]. In these patients, osteoglycin levels are associated with duration of type 2 diabetes, but not glycated hemoglobin A1c (HbA1c), fasting plasma glucose, NTX, or osteocalcin [32••]. These results indicate that osteoglycin influences bone formation, even though over-expression of osteoglycin relates to both increased osteoblastic differentiation and decreased osteoblastic differentiation. However, the study by Lee and colleagues shows an increase in bone mass among osteoglycin deficient mice [31••], and similarly, the one human study conducted suggests that osteoglycin is a marker of low bone mineral density and vertebral fractures [32••].

Osteoglycin in the Vascular System

Bone mediators can influence calcifications in the vascular system, where bone markers and regulators like osteocalcin, sclerostin, RANKL, and OPG promote or impair the development of vascular calcifications [33]. Osteoglycin may also influence the vascular system, and osteoglycin is suggested to influence bone diseases, cancer, cardiovascular disease, and neurological conditions [34]. Osteoglycin is identified as a component of the vascular extracellular matrix [35] and is expressed by cardiomyocytes [36, 37], cardiac fibroblasts, and vascular smooth muscle cells [38]. Vascular smooth muscle from normal human coronary arteries and human samples of advanced atherosclerotic lesions express osteoglycin, whereas neither endothelial cells nor macrophages express osteoglycin [35]. Furthermore, osteoglycin is not associated with the calcification in atherosclerotic plaques [35]. This is also reported in a study on essential hypertensive patients, where osteoglycin levels are not associated with carotid plaques [39]. In another study, osteoglycin deficient mice developed diastolic dysfunction as a result of cardiac fibrosis [40•]. This can be a result of an increased rate of fibroblastic proliferation which was observed in a line of immortalized human fibroblasts [40•]. Based on these pre-clinical studies, osteoglycin seems to be a part of the normal vascular system and could actually be important in the prevention of cardiovascular disease. However, in epidemiological studies investigating osteoglycin as a predictor of cardiovascular disease, a case-control study reports that circulating osteoglycin levels are associated with an increased risk of major cardiovascular events in patients within 1 year after coronary angiography [41]. Furthermore, osteoglycin is a predictor of all-cause mortality in a Korean prospective cohort of patients with chronic kidney disease with 56 months of follow-up [42•]. This finding is only present in the non-diabetes group [42•]. This suggests osteoglycin as a potential marker of cardiovascular disease despite the fact that osteoglycin may not be involved in the process of the cardiovascular disease per se.

Osteoglycin as a Metabolic Mediator

Osteoglycin may be a metabolically active proteoglycan as myoblasts express osteoglycin [23]. Vitamin D deficiency decreases the expression of osteoglycin from muscle in a diabetic mouse model and so, osteoglycin could be dependent on vitamin D [43•]. On the other hand active 1,25 Vitamin D increases osteoglycin expression in myoblastic cells [26]. Advanced glycation end products (AGE) decrease the expression of osteoglycin in myoblastic cells [26]; however, this was recovered by active Vitamin D. Thus, in muscle, osteoglycin could be expressed by a Vitamin D dependent mechanism. Furthermore, in overweight human individuals, osteoglycin is more abundant in visceral adipose tissue than in subcutaneous adipose tissue [44]. Osteoglycin may thus function in both muscle and fat tissue. The amount of white adipose tissue is increased in osteoglycin deficient mice. Furthermore, osteoglycin deficient mice display impaired glucose tolerance during both chow diet and high-fat diet. In these osteoglycin deficient mice, the impairment in glucose tolerance is associated with elevated insulin levels [31••]. During a glucose tolerance test on mice, osteoglycin treatment is related to a dose-dependent lowering of blood glucose levels. In vitro treatment with osteoglycin results in a dose-dependent increase in the expression of Ins1 and Ins2 mRNA [31••]. Ins1 and Ins2 are coupled to insulin secretion [31••]. Also, during insulin tolerance tests, osteoglycin treatment increases the decline in glucose levels in response to insulin, suggesting that the action of insulin is enhanced by osteoglycin [31••]. Thus, osteoglycin may be a metabolically active molecule. This could be reflected in patients undergoing gastric weight loss surgery or dietary-induced weight loss since surgery induces an increased osteoglycin level, which is associated with decreased fasting blood glucose. However, during weight loss, especially by gastric surgery, other mechanisms may also apply to the observed effects [45].

Conclusion

Osteoglycin is expressed in bone, muscle, vascular, and adipose tissues. Based on the current evidence, osteoglycin may be a mediator that influence bone negatively by a decrease in osteoblast differentiation and a decrease in bone mineral density. Furthermore, osteoglycin seems to be a metabolically active molecule that enhances the effect of insulin, and osteoglycin is present in the vascular system and may be a marker of vascular disease. Figure 1 illustrates the possible actions of osteoglycin. Antibodies have been developed for

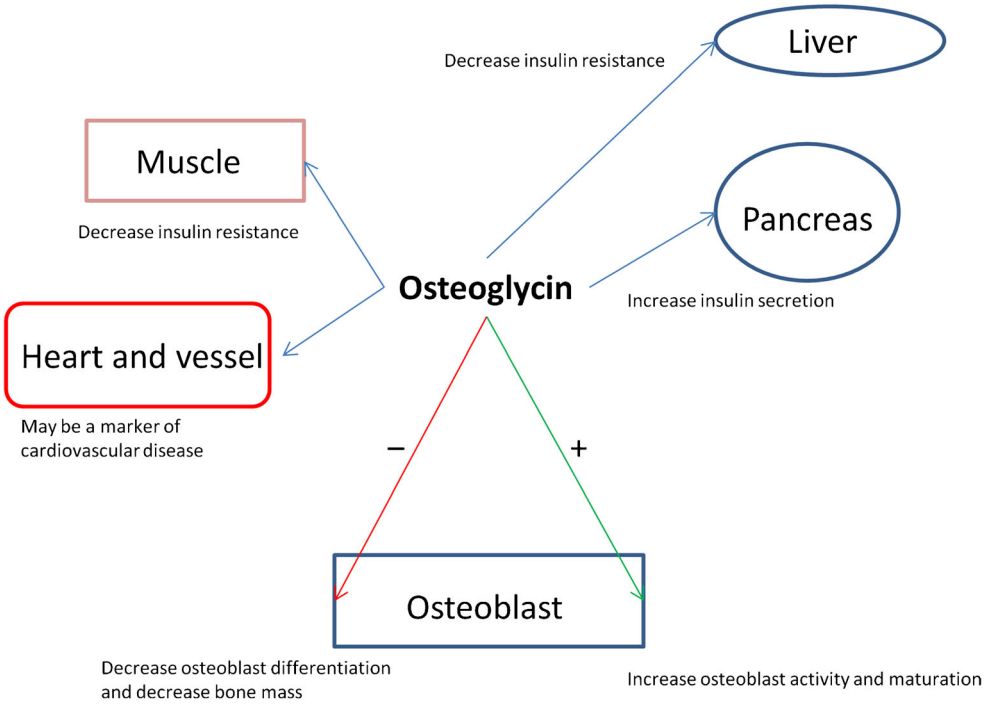

Fig. 1 Possible actions of osteoglycin. Osteoglycin is expressed in a variety of tissues including bone and muscle. Osteoglycin may increase insulin secretion in the pancreas and decrease insulin resistance in muscle and liver. In bone, osteoglycin may inhibit osteoblast differentiation and decrease bone mass, but other studies suggest that osteoglycin may increase osteoblast activity and maturation. Also, osteoglycin may be a marker of cardiovascular disease

the measurement of osteoglycin [46], and there are some osteoglycin assays available for measurement in humans. Osteoglycin seems to be independent of renal function as Tanaka and colleagues [32••] and Baek and colleagues [42•] report no association between osteoglycin levels and renal function reflected by creatinine and estimated glomerular filtration rate, respectively. Still, little is known about the dynamics of osteoglycin, including whether it is a stable molecule or has a short half-life and how it is metabolized in humans. Furthermore, the expression of osteoglycin could be regulated by factors such as the circadian rhythm, feeding, and exercise. The evidence from in vitro and animal models is limited, and very few studies have reported on osteoglycin in humans. Further research should examine the dynamics of osteoglycin and also investigate osteoglycin in humans and whether it is related to the diabetic state. Patients with type 2 diabetes have a higher fracture risk despite an increase in bone mineral density and decrease in bone turnover [47–49]. Insulin resistance has been hypothesized to contribute to these alterations in bone [50]. Theoretically, osteoglycin could be decreased in type 2 diabetes due to AGE production and accumulation. This would decrease osteoglycin expression and subsequently impair/decrease insulin sensitivity and increase bone mass (as reflected by bone mineral density). However, the bone would be brittle due to collagen fibrillogen deficits. In conclusion, osteoglycin may be a novel marker of a bone, muscle, and pancreatic axis. However, current evidence is limited and mainly supported by the recent study by Lee and colleagues [31••]. Further research investigating the dynamics of osteoglycin and clinical utility of osteoglycin is needed.

Compliance with Ethical Standards

Conflict of Interest Jakob Starup-Linde reports personal fees from Gilead Sciences Denmark and Eli Lilly Denmark.

Rikke Viggers and Aase Handberg declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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