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Possible role of osteoglycin levels in Diabetic Nephropathy Patients

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Abstract: Osteoglycin (OGN), also known as osteoinductive factor or mimecan, is a secretory protein belonging to class III of the small leucine-rich proteoglycans. OGN is a single-copy gene on the human 9q22.31 chromosome that produces three mRNA transcripts, three of which are the result of differential splicing inside the first translated ex. Because of proteolytic cleavage and glycosylation, different protein isoforms exist, whereas only one precursor protein is encoded. Osteoglycin may be a metabolically active proteoglycan as myoblasts express osteoglycin .Vitamin D deficiency decreases the expression of osteoglycin from muscle in a diabetic mouse model and so, osteoglycin could be dependent on vitamin D. 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 .Ins1 and Ins2 are coupled to insulin secretion .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. 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. serum OGN could act as an albuminuria-independent biomarker of incipient kidney dysfunction in T2D patients.

Keywords: *osteoglycin, Diabetic Nephropathy*

1.Introduction

Osteoglycin (OGN), also known as osteoinductive factor or mimecan, is a secretory protein belonging to class III of the small leucine-rich proteoglycans [1]. The extracellular matrix (ECM) is a complex network composed of an array of multidomain macromolecules organized in a cell-matrix network manner and plays an important role in physiology and pathophysiology [2]. The ECM is made up of noncellular components with specific functions in regulating cell behavior [2].

ECM components are now widely known to mediate and modify signal transmission and are also linked to a variety of illnesses, including cardiovascular and skeletal issues, fibrosis, and cancer [3].

Of particular interest are small leucine-rich proteoglycans (SLRPs), a group of ECM components involved in matrix structural organization. These molecules have been extensively studied for their ability to bind collagen and their roles in tissue association, fibrosis, and wound repair [4].

SLRPs are made and secreted in the pericellular spaces, where they are eventually integrated into the ECM of the tissue [4]. Because of the diversity in their leucine-rich repeat (LRRs) cores and glycosylation patterns, SLRPs can bind several growth factors, such as the insulin like growth factor receptor (IGFR), epidermal growth factor receptor (EGFR), and transforming growth factor-β (TGF-β) [5].

Therefore, in addition to being an important structural component of the ECM, SLRPs have been implicated in the complex network of the cells' 'inside-out' signal transduction and participate in a wide range of processes such as inflammation, atherosclerosis, and tumorigenesis, which are critical for many processes [6]. OGN, a class III member of the SLRP family, was isolated from bone and originally called osteoinductive factor [7]. Among a group of proteins identified as important regulatory proteins within the ECM, OGN is expressed in a variety of organs and has effects on bone formation [7,8], fibrillogenesis, tumorigenesis, and pathological processes, including vascular differentiation and remodeling [7]. This molecule is also implicated in connective tissue-related diseases [7].

OGN—Structure and Functions:

The overall structure of SLRPs consists of a core protein composed of LRRs and an N-terminal cysteine-rich cluster bound to specific glycosaminoglycans (GAG) [9].

OGN, a class III SLRP with numerous glycosylation sites, has a unique cysteine-rich region sequence as well as six LRRs (Figure 1). Structurally, OGN can be glycosylated to a defined level, and that adds glycosaminoglycans (GAG) and glycans to proteins in the endoplasmic reticulum (ER) and Golgi apparatus, allowing them to perform a variety of functions [10].

The GAG chains are believed to function in the maintenance of interfibrillar spacing and normal tissue hydration [11]. Because of differential splicing, alternative polyadenylation, and posttranslational modifications, OGN mRNA and proteins of different sizes have been identified [11].

Additionally, OGN is a single-copy gene on the human 9q22.31 chromosome that produces three mRNA transcripts, three of which are the result of differential splicing inside the first translated ex. Because of proteolytic cleavage and glycosylation, different protein isoforms exist, whereas only one precursor protein is encoded [12].

The full-length OGN cDNA was identified during establishment of the gene expression profile in the human pituitary gland (GenBank no. AF100758) [13].

A conserved consensus p53-binding DNA sequence in the first intron of the human OGN gene was validated, and p53 can activate OGN expression via this binding sequence. Thus, OGN has been accepted as a direct target gene of p53 [14]. UV-responsive E-box and several interferon-stimulated response elements (ISREs), which have been identified and demonstrated to operate as positive regulators of the human OGN promoter, were also found in the promoter region of the bovine and human OGN genes [15].

Figure 1. Basic structure of an OGN. KS: keratan sulphate; GAG: glycosaminoglycans; N: amino terminal; C: carboxyl terminal; LRR: leucine rich repeat motifs.

OGN was found in a variety of tissues, including the cornea, skin, aorta, sclera, vagus nerve, and cartilage, as well as at lower levels in the ovary, cerebellum, skeletal muscle, heart, and kidney [16]. Additionally, post-translational modifications of the protein increase the diversity of OGN, and a higher level of functional diversity is achieved this way [16].

OGN is secreted into the ECM after post-translational modification, where it interacts with a variety of molecular targets and plays a variety of biological roles. Fibrillar collagens, growth factors, and ECM molecules are examples of cell membrane receptors. As a result, ECM assembly and immunity can be influenced. Its functions were subsequently extended to include corneal transparency, fibrosis, and cancer biology [17].

OGN is involved in several biological processes and is related to various pathologies, such as bone fragility, cardiovascular disease (CVD), neurologic disease, ocular diseases, and chronic kidney disease (CKD), among others [17].

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 [18].

Bone turnover is a coupled process of bone resorption and bone formation [19]. Osteoclasts perform the bone resorption by adhering to the underlying bone and secreting acidic proteases that degrade bone [20].

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 [21].

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 [22].

The active 1,25 vitamin D stimulates differentiation of osteoclasts and regulates the mineralization of bone. RANKL is produced by the osteoblasts and promotes differentiation, activation, and survival of osteoclasts [22].

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. Sclerostin is an inhibitor of the Wnts, which are small proteins that stimulate osteoblast differentiation and promote bone formation [23].

Osteoglycin and Bone

Osteoglycin was first identified in bovine bone and thought to promote bone formation. Osteoglycin is monogenic expressed by several tissues such as bone, cartilage, cornea, and aorta in bovine [24].

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. Samples from muscle tissue were not examined in these studies [25]. Osteoglycin is also expressed in human mesenchymal progenitor cells, in which osteoglycin expression increased following exposure to Osterix [25].

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 [26].

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 [27].

Osteocalcin and alkaline phosphatase are products released by osteoblasts and are indices of bone formation but also of osteoblastic differentiation [28].

Similarly, in osteoblastic cell lines, a reduction in endogenous osteoglycin levels show opposite effects compared to osteoglycin over-expression [27].

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 [29].

Osteoblastic cells present high levels of alkaline phosphatase when exposed to a conditioned medium from the myoblastic cells that over-express osteoglycin. 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 [30].

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 [30].

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 [31].

In osteoglycin deficient mice, collagen fibrillogens are abnormal and increased in size compared to wild type mice [32]. 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 [32].

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 [33]. While the study from Tasheva and colleagues [32] reports no improvement in bone with x-ray assessment, Lee and colleagues, 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 suggests that osteoglycin is a negative regulator of osteoblast activity; nevertheless, evidence is conflicting [33].

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 [34]. In these patients, osteoglycin levels are associated with duration of type 2 diabetes, but not glycated hemoglobin A1c (HbA1c), fasting plasma glucose, or osteocalcin [34]. 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 [33], and similarly, the one human study conducted suggests that osteoglycin is a marker of low bone mineral density and vertebral fractures [34].

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 [35].

Osteoglycin may also influence the vascular system, and osteoglycin is suggested to influence bone diseases, cancer, cardiovascular disease, and neurological conditions [36].

Osteoglycin is identified as a component of the vascular extracellular matrix and is expressed by cardiomyocytes, cardiac fibroblasts, and vascular smooth muscle cells [37]. 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 [37].

Furthermore, osteoglycin is not associated with the calcification in atherosclerotic plaques. This is also reported in a study on essential hypertensive patients, where osteoglycin levels are not associated with carotid plaques [38].

In another study, osteoglycin deficient mice developed diastolic dysfunction as a result of cardiac fibrosis. This can be a result of an increased rate of fibroblastic proliferation which was observed in a line of immortalized human fibroblasts [39].

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 [40].

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 [41]. This finding is only present in the non-diabetes group [41]. 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 [41].

Osteoglycin as a Metabolic Mediator

Osteoglycin may be a metabolically active proteoglycan as myoblasts express osteoglycin [27]. Vitamin D deficiency decreases the expression of osteoglycin from muscle in a diabetic mouse model and so, osteoglycin could be dependent on vitamin D [42].

On the other hand, active 1,25 Vitamin D increases osteoglycin expression in myoblastic cells. Advanced glycation end products (AGE) decrease the expression of osteoglycin in myoblastic cells [27]. 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 [43].

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 [33].

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. Ins1 and Ins2 are coupled to insulin secretion [33]. 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 [33]. 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 [44].

Osteoglycin (OGN), also known as osteoinductive factor or mimecan, is a secretory protein belonging to class III of the small leucine-rich proteoglycans [45]. OGN is involved in several biological processes [46,47,48] and is related to various pathologies, such as bone fragility, cardiovascular disease (CVD), neurologic disease, ocular diseases, and chronic kidney disease (CKD), among others [46,47]. OGN has a tissue-specific glycosylation site and different post-translational modifications [49] related to its functional role in different locations [46]. OGN participates mainly as a regulator of bone metabolism [50,51], as it is a bone-associated glycoprotein, expressed by osteoblasts [52,53]. Moreover, OGN is a basic component of the vascular extracellular matrix, which is expressed by cardiomyocytes, cardiac fibroblasts, and vascular smooth muscle cells [54,55].

Diabetic kidney disease (DKD) is one of the most frequent complications of type 2 diabetes (T2D). The classic description of DKD involves progressive stages of glomerular hyperfiltration, microalbuminuria, overt proteinuria, and a decline in the estimated glomerular filtration rate (eGFR) [56]. It was widely accepted that patients with DKD develop albuminuria before a decrease in the eGFR. However, these concepts have been increasingly challenged as evidence suggests that DKD is presented in a more heterogeneous manner. Large cross-sectional studies have revealed that a significant proportion of T2D patients with impaired kidney function determined by decreased eGFR values present normal levels of albuminuria [57,58,59,60,61,62]. Therefore, determining biomarkers associated with impaired eGFR could be a useful measurement to analyze the progression to DKD in T2D patients.

Few and contradictory results are known regarding OGN levels in T2D patients with DKD [63,64]. In these studies, OGN was suggested to be a sensitive marker for early microalbuminuria; however, there is no consensus on the level of this protein in T2D patients with DKD compared to healthy subjects. Little is known regarding the serum levels of OGN in T2D and control subjects with contradictory results. The increased levels of serum OGN observed in T2D patients compared to healthy controls, especially in those with decreased eGFR values agree with the findings reported by Wang et al., who found increased concentrations of OGN in T2D patients with diabetic nephropathy compared to T2D patients without diabetic nephropathy and healthy controls [63]. In contrast, Wei et al. reported that the decline of serum OGN levels was closely related to the development and pathogenesis of diabetic nephropathy suggesting that low serum OGN levels could act as an independent diagnostic marker of diabetic nephropathy associated with microalbuminuria in T2D patients [64]. Similarly, a study in mice with CKD showed that decreased serum OGN level was positively associated with impaired kidney function [65]. The aforementioned studies associate the OGN serum levels with kidney status independently of the presence of T2D.

The higher levels of FGF-23 in T2D patients compared to control subjects could partly explain the elevation of serum OGN in this group. Consistently, studies reported increased FGF-23 serum levels in the T2D population [66,67]. The presence of T2D implies a progressive deterioration of kidney function, which is associated with increased serum levels of FGF-23 and iPTH as observed in the T2D subjects with an incipient decrease in glomerular filtration. The elevation of iPTH in these patients could be explained by its positive correlation with FGF-23 as has been reported in CKD patients [68,69]. However, a review addressing the role of FGF-23 in clinical outcomes in T2D patients has shown that the mechanism by which an increase in FGF-23 occurs in T2D patients is unclear [70]. Most studies suggest that the increase in FGF-23 may be associated with the presence of CVD and may act as a predictor of cardiovascular mortality in the T2D population [71,72].

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