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Review

Traditional bone matrix proteins in obesity, insulin resistance and diabetes: state of the art and perspectives

Mihai A. Goia-Socol, Monica Goia-Socol, Carmen E. Georgescu
Endocrinology Chair, VIth Medical Sciences Department, "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, Romania.

Abstract. Osteocalcin (OCN), osteonectin (ON) and osteopontin (OPN) are proteins included in the bone matrix. Bone development and maintenance of bone functions represent main tasks, but they are also involved in energy and glucose metabolism. The aim of this review is to summarize the roles of these proteins in obesity, insulin resistance and type 2 diabetes (T2DM). Circulating OCN exhibits biological effects on pancreatic β-cells and adipose tissue. Undercarboxylated OCN isoforms are hormonally active, stimulating insulin secretion and increasing insulin sensitivity in muscles and adipose tissue. Leptin and insulin are involved in bone OCN secretion acting as a feed forward loop between the undercarboxylated OCN and insulin. OPN is secreted by adipocytes and may play a pivotal role in obesity and T2DM by linking obesity to insulin resistance development. This pathological process is started by inflammation initiation and macrophages accumulation in adipose tissue. ON is mainly expressed in adipocytes. The level of expression varies during adipogenesis stages (high during promotion of cell differentiation to adipogenic lineage, low at the beginning of adipocyte cell differentiation and high in mature adipocytes); this suggests a potential role in lipid storage in the extracellular matrix of adipose tissue. ON was also correlated with dyslipidemia, and can act as an independent determinant of insulin resistance in late pregnancy, suggesting a positive correlation between ON levels and inflammation. Potential novel therapies targeting OCN, ON and OPN regulation could represent promising approaches for prevention and treatment of T2DM, obesity, insulin resistance and related metabolic outcomes.

Key Words: bone matrix proteins, obesity, insulin resistance and diabetes mellitus.

Corresponding Authors: M.A. Goia-Socol, e-mail: goia.mihai@umfcluj.ro

Introduction

The organic and inorganic components of bone are organized in a complex system and have fundamental structural and functional roles. Of the organic components, collagen accounts for around 90%, while matrix proteins, proteoglycans, cytokines and growth factors account for around 10%. The main proteins included in the bone matrix are osteocalcin (OCN), osteonectin (ON), osteopontin (OPN) and osteoprotegerin (OPG). In addition to their key roles in bone development and function, recent studies suggest that these proteins may play an important role in the global energy balance and glucose metabolism, and thereby in obesity, insulin resistance, type 2 diabetes (T2DM) and the polycystic ovary syndrome and, at least some of them, might be linked to increased cardiovascular risk (Pepene et al 2011). Nowadays, these morbid conditions affect many people worldwide leading to increased morbidity and mortality due to the related complications (You et al 2013).

Given this, the aim of this review is to summarize the role of main bone matrix proteins involved in obesity, insulin resistance and T2DM.

Osteocalcin

OCN is a noncollagenous protein of the bone matrix. Its main biological role is bone mineralization and calcium homeostasis, but has also been associated with glucose metabolism and some hormonal actions (Zhong et al 2015, Zanatta et al 2014, Abdallah et al 2015). OCN is produced by osteoblasts, osteocytes and odontoblasts, and can undergo γ-carboxylation. The γ-carboxylated forms bind hydroxyapatite and are found in the bone extracellular matrix, while the majority of the undercarboxylated forms are released in the circulatory system. The latter act as a positive regulator of glucose homeostasis (Zanatta et al 2014).

Multiple studies suggest that the circulating OCN exhibits biological effects on pancreatic β-cells and adipose tissue. Undercarboxylated isoforms of OCN are hormonally active, stimulating insulin secretion and increasing insulin sensitivity in muscles and adipose tissue. Leptin and insulin are involved in OCN secretion in bone, acting as a feed forward loop between the undercarboxylated OCN and insulin (Zanatta et al 2014). In this mechanism, the endocrine skeleton plays an important role in energy metabolism regulation (Abdallah et al 2015).

Multiple studies conducted in humans analyzed the associations of OCN circulating levels with T2DM and related metabolic phenotypes such as the polycystic ovary syndrome (Pepene 2013). In Chinese post-menopausal women, the level of circulating OCN was inversely associated with visceral fat (Luo et al 2015). Following a systematic review of the published literature, decreased levels of serum OCN were identified in patients with T2DM and metabolic syndrome. Cross-sectional studies

analysis revealed an inverse association between OCN levels and T2DM risk in models adjusted for fasting plasma glucose (FPG) and fasting insulin. Increased levels of serum OCN were found to be associated with a significant increase of homeostasis model assessment β-cell function (HOMA-B) and reduction of glycated hemoglobin (HbA1c) in both cohort and cross-sectional studies; a significant FPG levels, HOMA-insulin resistance (IR), and body mass index reduction was observed in the latter studies only. Similar results were published in animal work. However, in animals, elevated OCN levels were not associated with fasting insulin (Kunutsor et al 2015).

Recent studies assessed the role of Delta like-1 (Dlk1), an endocrine regulator of bone turnover, in insulin signaling in osteoblasts and energy metabolism. In humans, it was shown that undercarboxylated OCN stimulates Dlk1 expression by the pancreas. In the Dlk1-deficient mice model it was observed that circulating levels of undercarboxylated OCN and insulin sensitivity increased, whereas mice overexpressing Dlk1 in osteoblasts had decreased insulin secretion and sensitivity. These findings suggest that β-cells may act as a negative feedback mechanism to countervail the stimulatory effect of insulin on undercarboxylated OCN production in the osteoblast; this mechanism may play a key role in OCN-induced hypoglycemia (Abdallah et al 2015).

In preclinical studies it has been shown that OCN influences glucose metabolism. In OCN knock-out mice decreased insulin secretion, glucose tolerance, insulin sensitivity and obesity were observed following normal diet administration; decreased number of pancreatic islets, β-cell area and mass, and insulin production were also recorded (Lee et al 2007). These pathophysiological processes where shown to be reversed by OCN administration (Zanatta et al 2014). A study conducted in the Gprc6a knockout mice model suggested that the mechanism involved in OCN regulation of insulin biosynthesis and pancreatic β-cell proliferation is based on the OCN possibility to bind the Gprc6a receptor and increase insulin production (Pi et al 2011). In addition, different studies showed that OCN regulates the fat mass in OCN knockout mice under normal diet, but the exact mechanism is currently unknown (Ferron et al 2008). The presumptions are that the potential of OCN to induce adiponectin expression and to interact with Gprc6a on adipocytes may contribute to reduction of body fat mass in mice, but further studies need to be performed (Ferron et al 2014).

The relationship between vitamin K and OCN has recently been discovered, with possible implications in obesity-insulin resistance determination. Vitamin K and its reduction by a second enzyme, a reductase called VKORC1 (subunit 1 of the vitamin K epoxide reductase complex), is essential for the γ-carboxylation of OCN before being secreted by osteoblasts in the bone extracellular matrix. The process of γ-carboxylation was proven to inhibit OCN endocrine functions, as previously mentioned, undercarboxylated OCN being the hormonally active isoform of the protein (Ferron et al 2015).

VKORC1 gene polymorphisms have been studied in various populations, including Romanians (Buzoianu et al 2012, Şuteu et al 2012) in relation to deep vein thrombosis susceptibility (Vesa et al 2015) and as a pharmacogenetic tool to predict sensitivity and therapeutic response to warfarin (Militaru et al 2012, Buzoianu et al 2013). The same VKORC1 gene polymorphisms were recently linked to vascular calcification susceptibility (Teichert et al 2008) and elevated triglycerides (Georgescu et al 2013).

Another key element in this process is γ-glutamyl carboxylase (GGCX), an enzyme that catalyzes the conversion of glutamic acid to γ-carboxyglutamic acid.

In osteoblast-specific GGCX-deficient mice serum, glucose levels could be maintained with low amounts of insulin, and the weight of white adipose tissue significantly decreased, suggesting that GGCX expressed in osteoblasts is critical for the maintenance of blood glucose and weight of white adipose tissue (Shiba et al 2014).

In human studies, vitamin K supplementation for 4 weeks increased the serum levels of carboxylated OCN and decreased those of undercarboxylated OC without altering total OCN and increased serum adiponectin but not leptin concentrations. It did not affect insulin resistance in premenopausal and prediabetic women but, in contrast to the experimental results, had beneficial effects on glycemic status and insulin sensitivity (Rasekhi et al 2015a, Rasekhi et al 2015b). Thirty-six months vitamin K supplementation determined a significant reduction of HOMA-IR (Yoshida et al 2008). It remains to be studied why vitamin K supplementation, which decreases undercarboxylated OCN percentage and thus would be expected to worsen insulin sensitivity, has opposite results. It may be speculated that adiponectin, an adipokine with insulin-sensitizing and anti-inflammatory properties, may contribute to this effect.

Developing therapies targeting γ-carboxylation of OCN could improve insulin sensitivity and hence the glycemic control in type 2 diabetic patients.

Osteopontin

OPN is a phosphoprotein found in different types of cells (Zhong et al 2015). It is mainly expressed in bone, large amounts (0.1-0.2%) being found in the collagenous extracellular matrix. It has a mechanical role in energy dissipation mechanism of the bone by acting as a glue for the bone matrix (Sroga et al 2012). The main biological role of OPN is bone modeling and remodeling, but it is also involved in pathophysiological processes such as wound healing, inflammation, neoplastic transformation and cardiovascular function. (Zhong et al 2015). OPN implication in arterial calcification has to be noted. The protein is present in the calcified atherosclerotic plaques (but not in normal arteries) and its expression was positively corelated with their progression (Luna-Luna et al 2015).

Recent studies have shown that OPN is also secreted by adipocytes and that it may play a pivotal role in obesity and T2DM by linking obesity to insulin resistance development. This pathological process is started by onset of inflammation and macrophages accumulation in the adipose tissue (Zhong et al 2015). In patients with insulin resistance and T2DM, the positive regulators of OPN expression associated with insulin resistance are the cytokines IL-1b, IL-6, INF-c, TNFα, LPS, reactive oxygen species, leptin and angiotensin II, and hypoxia. The negative regulators were found to be PPARγ and/or LXR ligands because they antagonize OPN expression. A similar role for OPN was suggested by different studies on macrophage models, mouse aorta and fibroblasts models (You et al 2013). OPN effects are enhanced by the cleavage of matrix metalloproteinases (MMP).

This phenomenon occurs in adipocytes of obese patients leading to increased pro-inflammatory and pro-diabetic activity of OPN (Leitner et al 2015). In addition, following OPN splicing into the OPNa, OPNb and OPNc isoforms, an association between the level of serum OPNc and diabetes and/or obesity was observed (Sarosiek et al 2015).

The patients diagnosed with obesity/insulin resistance and T2DM have a subclinical systemic inflammation (Daniele et al 2014). In obese, this type of inflammation appears due to macrophage-derived OPN accumulated in adipose tissue, and induction of local and systemic insulin resistance (Ahlqvist et al 2013).

In a study conducted by Catalán et al (2015) high levels of OPN were also observed as well as its expression in the peripheral blood mononuclear cells (PBMC) suggesting the role of OPN in the inflammatory status in obesity. This type of inflammation is associated with both hyperglycemia and insulin resistance in diabetic patients (Daniele et al 2014). In a preclinical study, it has been shown that OPN deficiency, regardless of body composition, decreases adipose tissue inflammation, improves glucose tolerance, and reduces insulin resistance in mice (Kahles et al 2014). In rats, OPN expression in primary adipocytes is stimulated by glucose-dependent insulinotropic polypeptide (GIP), which is also knows as a stimulator of adipogenesis (Ahlqvist et al 2013). However, in humans, it was observed that a genetic variant with decreased GIP receptor function is associated with reduced OPN expression and improved insulin sensitivity (Kahles et al 2014). In addition, in the study conducted by Zhong et al (2015), it has been shown that OPN may induce adipogenesis of brown adipocytes from white adipocytes; these findings could have a significant importance because brown adipocytes are contributing to weight loss.

Furthermore, in OPN knockout (OPN-KO) mice protection from insulin resistance was reported following 2–4 weeks of high fat diet compared to wild-type mice (control); OPN may play an important role in the high fat diet-induced insulin resistance because of the changes in adipocyte biology and the local inflammation related to OPN overexpression in adipose tissue and local macrophages, respectively (You et al 2013). Another study showed that OPN-KO mice, compared to wild-type mice, develop high insulin sensitivity, have lower body weight and fat mass following high-fat diet administration, display reduced fibrosis in adipose tissue and liver, and reduced oxidative stress in adipose tissue (Lancha et al 2014a).

Surprisingly, in humans, the surgically induced weight loss did not determined changes of OPN concentration in serum, epididymal adipose tissue, and liver in rats (Lancha et al 2014c). Similar results were found in obese patients diagnosed with T2DM and insulin resistance. However, in humans it was observed that dietary weight loss significantly reduces circulating levels of OPN (Kahles et al 2014), but no correlation between OPN concentration and the percentage of body fat was observed (Kahles et al 2014). In addition, in obese patients who underwent Roux-en-Y gastric bypass (RYGB) increased OPN concentrations were observed compared to patients with sleeve gastrectomy, in whom OPN levels remained unaltered. This could be due to the increased bone resorption following RYGB procedure (Lancha et al 2014b).

Osteonectin

ON, also known as secreted protein acidic and rich in cysteine (SPARC), is a protein of bone matrix secreted by osteoblasts during bone formation. It is also expressed by a large variety of cell types: chondrocytes, fibroblasts, adipocytes, platelets, epithelial cells etc. Its main biological function is extracellular matrix modeling. This function is accomplished by its influence on the changes that are necessary for cells migration and proliferation. Because of the role in cell shape changes and probably in other unknown mechanisms, ON is considered a cell survival molecule as long as cell apoptosis is also preceded by shape changes, mainly rounding (Bradshaw 2012).

In humans, mRNAs encoding ON were identified in adipose tissue depots. ON expression was found to be higher in adipocytes compared to the stromal vascular fraction. Its level of expression varies in different stages of adipogenesis as follows: high during promotion of cell differentiation to adipogenic lineage, low at the beginning of adipocyte cell differentiation and high in mature adipocytes. This variation suggests that ON may play a role in the lipid storage in the extracellular matrix of the adipose tissue (Chavey et al 2006). An in vitro study conducted in a human-derived adipocyte cell line showed that overexpression of ON in humans' adipocyte cells causes insulin resistance, mitochondrial dysfunction, influences expression of some pro-inflammatory cytokines, inhibits insulin-stimulated glucose transport, decreases GLUT-4 expression in adipocytes and increases reactive oxygen species production (Shen et al 2014). In mature adipocytes, ON is contributing to insulin resistance by increasing the expression of proinflammatory cytokines TNF, IL-6, IL-3 and IL-10. ON production in adipose tissue is regulated by leptin and insulin, which increase ON level in a dose-dependent way, while glucose administration decreases ON levels (Kos et al 2009).

In obese patients, ON serum levels were found to be positively associated with obesity indices and insulinemia (Sroga & Vashishth 2012, Minchenko et al 2013). In obese men with glucose intolerance, ON overexpression was also identified in subcutaneous tissue (Minchenko et al 2013), while in patients with newly diagnosed T2DM increased levels of serum ON were recorded (Wu et al 2011). In women diagnosed with gestational diabetes mellitus higher levels of ON and lower levels of adiponectin compared to subjects with normal glucose tolerance were recorded. These findings suggest the positive correlation between ON levels and inflammation, and that ON may be correlated with dyslipidemia, representing an independent determinant of insulin resistance in late pregnancy (Xu et al 2013). Significant decreases of serum ON concentrations were recorded following bariatric surgery, suggesting that weight loss following bariatric surgery may modify the extracellular environment due to some related metabolic changes (Lee et al 2014).

In animal studies, ON overexpression in adipose tissue in rats receiving high-fat diet during a period of 12 weeks was observed (Shen et al 2014). In ON knockout mice increased amounts of adipose tissue compared to the control were recorded (Nie et al 2011).

ON expression was also identified in pancreatic β-cells. In healthy donors, ON level was positively associated with glucose-stimulated

insulin secretion of β-cells. In hyperglycemia statement, ON overexpression in β-cells leads to 2.4-fold increase of insulin secretion. These findings suggest that ON is involved in insulin secretion regardless of insulin resistance induced by obesity. It was demonstrated that ON acts as a gene regulator for pancreatic cell genesis, growth and survival (Harries et al 2013). Table 1 summarizes the potential perspective applications of OCN, OPN and ON in obesity, insulin resistance and T2DM.

Table 1. Potential perspective applications of bone matrix proteins in obesity, insulin resistance and diabetes

Bone matrix protein	Perspective
Osteocalcin	o Prevention and treatment of obesity and T2DM o Marker for prevention and treatment of T2DM
Osteopontin	o Prevention and treatment of obesity and T2DM: - Targeting the promotion of brown adipogenesis - OPN inhibition - treatment for obesity and fatty liver o Marker for cardiovascular complications of obesity
Osteonectin	o Treatment for obesity and insulin resistance

Conclusions and perspectives

In the future, OCN may be considered as an option for the prevention and treatment of obesity and T2DM, and other related metabolic outcomes (Kunutsor et al 2015). Potential novel approaches for prevention and treatment of obesity and T2DM could be developed based on OPN and its analogs by targeting the promotion of brown adipogenesis from white preadipocytes, (Zhong et al 2015) and by targeting reduction of MMP cleavage of OPN (Leitner et al 2015). The first step for developing this type of therapies is understanding the mechanism underlying the pathophysiological processes and the functional role of OPN isoforms (Sarosiek et al 2015). OPN inhibition is a promising therapeutic approach for obesity and fatty liver treatment, (Lancha et al 2014a), and OPN monitoring might be a useful tool for assessment of the outcomes following clinical interventions for cardiovascular diseases related to obesity (Gómez-Ambrosi et al 2007). Given that ON is involved in obesity-induced adipose insulin resistance it may serve as a potential novel approach for obesity and obesity-related insulin resistance treatments (Shen et al 2014).

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Authors

•Mihai A. Goia-Socol, Endocrinology Chair, 6th Medical Sciences Department, "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, 3-5 Louis Pasteur Street, Cluj-Napoca, Cluj, 400349, Romania, EU, e-mail: goia.mihai@umfcluj.ro

•Monica Goia-Socol, Endocrinology Chair, 6th Medical Sciences Department, "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, 3-5 Louis Pasteur Street, Cluj-Napoca, Cluj, 400349, Romania, EU

•Carmen E. Georgescu, Endocrinology Chair, 6th Medical Sciences Department, "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, 3-5 Louis Pasteur Street, Cluj-Napoca, Cluj, 400349, Romania, EU

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