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REVIEW ARTICLE

Protective role of osteocalcin in diabetes pathogenesis

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Abstract

In diabetes, metabolic, inflammatory, and stress-associated alterations conduce to ß-cell failure and tissue damage. Osteocalcin is a bone protein with several endocrine functions in different tissues. In this review, we gathered scientific evidence of how osteocalcin could modulate functional disorders that are altered in diabetes in an integrative way. We include adipose tissue, pancreatic function, and oxidative stress aspects. In the first section, we focus on the role of inflammatory mediators and adiponectin in energy homeostasis and insulin sensitivity. In the following section, we discuss the effect of osteocalcin in metabolic and pancreatic function and its association in insulin signaling and in ß-cell proliferation. Finally, we focus on osteocalcin action in oxidative and endoplasmic reticulum stress, and in antioxidant regulation, since ß-cells are well known by its vulnerability to stress damage. These evidences support the notion that osteocalcin could have an important role in diabetes treatment.

Keywords Diabetes · Bone metabolism · Osteocalcin · Oxidative stress

Introduction

Diabetes is characterized for the lack of insulin secretion and/or the decrease in insulin sensitivity. In diabetes, genetic and environmental factors have a crucial role in the vulnerability of pancreatic cells to the loss of function and destruction of ß-cells, this condition develops as a consequence of multiple metabolic alterations, inflammatory, hormonal, and stress-related effects [1–3].

In obesity, the disturbed remodeling of adipose tissue triggers changes in its secretory and metabolic activity, these changes induce the release of metabolites and adipokines that perturbed the inflammatory balance and the integration of signals in the adipose tissue [4]. Macrophages recruited are an important source of pro-inflammatory cytokines, which in turn, are associated with adipokines (leptin and adiponectin) imbalance [5]. Adipose tissue cytokines act systemically to inhibit insulin secretion and sensibility, among these are: TNFα, IL1ß, IL6, and IL10 [6,7].

Abnormalities in insulin secretion and sensitivity, trigger metabolic, inflammatory, and stress-associated alterations [8], these are associated with pancreas long-term functional overload that produces in consequence ß-cell failure [9]. Finally, prolonged hyperglycemia induces tissue damage and eventually leads to the development of complications [8].

Osteocalcin is the most abundant non-collagenous bone protein. Osteocalcin, in their undercarboxylated form (ucOCN), has proved to have several endocrine functions in different tissues, including pancreas, adipose tissue, muscle, and liver. Osteocalcin functions have proposed to be conducted through receptor GPRC6A [10,11].

Osteocalcin has demonstrated to be able to improve pancreatic and adipose tissue function and metabolic, inflammatory, and oxidative parameters, which are all affected in diabetes (Fig. 1) [12,13]. Furthermore, there is a feedback loop between insulin and osteocalcin, where both encourage the production of each other [14–16].

One of the biggest challenges of diabetes treatment is to preserve residual ß-cell function [12]. In this order, the results of the effects of osteocalcin in animal models, spur

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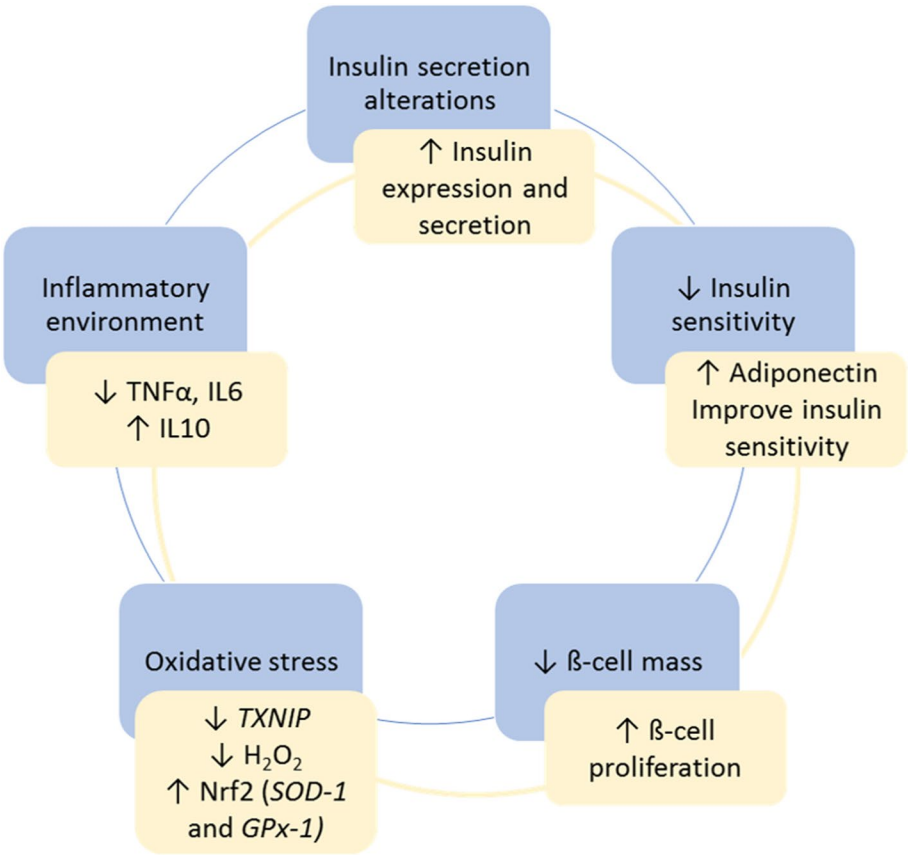

Fig. 1 Schematic representation of diabetes alterations and osteocalcin effects. In diabetes, several metabolic alterations are common; the blue frame indicates metabolic alterations of diabetes pathogenesis, while the yellow frame, indicates functions of osteocalcin that could contrast metabolic alterations of diabetes

the evaluation of their use as a potential and integral treatment for diabetes [17,18].

Adipose tissue interaction

Besides storing energy, adipose tissue secretes a variety of proteins that influence metabolism [19]. In obesity, the disturbed remodeling of adipose tissue triggers changes in its secretory and metabolic activity enhancing the release of metabolites and adipokines that perturbed the inflammatory balance [4]. Adipose tissue hypertrophy is associated with macrophage recruitment, which is an important source of pro-inflammatory cytokines such as TNFα, IL6, IL1ß, and monocyte chemoattractant protein 1 (MCP1). These pro-inflammatory mediators have been associated with the development of insulin resistance, also the imbalance in the adipokines leptin and adiponectin could underlie the link between insulin resistance and inflammation [5]. Oxidative stress, high blood glucose levels, fat intake, and dyslipidemia are all known to inhibit adiponectin secretion in vitro [20].

Adiponectin (also called Acrp30, apM1, or adipoQ) is a protein containing 244 amino acid residues that exist as a trimer, hexamer, and as small proteolytic cleavage products in both human and mouse. Adiponectin has been considered to be synthesized mostly by the adipose tissue, but it is also expressed in osteoblastic cells although in lower concentrations [21]. Adiponectin stimulates osteoblast proliferation and differentiation [22] and has been proposed to play a key role in the regulation of energy homeostasis and insulin sensitivity [21].

In mice fed with high fat diet (HFD), the expression of adiponectin in serum and white adipose tissue (WAT) decreased, additionally, animals presented metabolic disturbances like hyperglycemia and hyperinsulinemia. In mice models of obesity and type 2 diabetes, the administration of adiponectin improves metabolic parameters of insulin resistance, and the combination of adiponectin and leptin reverse completely insulin resistance [19]. Adiponectin prevents ß-cell apoptosis and promotes ß-cell regeneration through the induction of the expression of the gene, Nuclear receptor subfamily 2, group A, member 1 (*HNF4A*) [23].

It has been proposed that in humans, blood adiponectin levels were significantly lower in overweight vs. normal-weight subjects, reduced adiponectin blood levels are correlated with the presence of obesity-related complications including coronary diseases [4,21]. Moreover, adiponectin–resistin (AR) index has been proposed as an indicator of metabolic risk in

obesity, this index was found to positively correlate with risk of metabolic syndrome and type 2 diabetes development [4].

On the other hand, serum osteocalcin levels are related with blood adiponectin levels. Osteocalcin has demonstrated to increase the production of adiponectin [24]. Osteocalcin and ucOCN were able to increase adiponectin secretion in rat isolated adipocytes and whole adipose tissue, both decreased TNFα secretion by 62 and 72% respectively, but only osteocalcin decreased IL6 secretion in isolated adipocytes of rat. Furthermore, both forms significantly increased secretion of the anti-inflammatory cytokine IL10 in whole adipose tissue [25]. The pro-inflammatory cytokines, TNFα and IL1ß, are key elements in the islet inflammatory microenvironment. IL1ß has demonstrated to suppress the expression of genes associated with fully differentiated ß-cell phenotype, these alterations result in ß-cells that express and secrete both insulin and glucagon, and affect the overall function of pancreatic ß-cells [18].

Osteocalcin has demonstrated to be able to act directly on peripheral tissues specifically in muscle and adipose tissue to regulate glucose metabolism and insulin sensitivity [25,26]. ucOCN has shown to suppress lipolysis in WAT, to promote mitochondria biogenesis in muscle, and to stimulate the expression of genes involved in thermogenesis (*PGC1α* and *UCP1*) in brown adipocytes [10,11,27]. However, a study using a ß-catenin deletion mouse model showed that the decreased fat accumulation and increased metabolic level was dependent of bone mass, but it was not dependent upon osteocalcin, indicating that bone could secrete more hormones to regulate energy metabolism [13].

Adipocytes and osteoblast share a feedback loop where adiponectin can induce osteoblast proliferation and differentiation [22], adiponectin exerts its effects through brain signaling and by the sympathetic tone [28]. Adipocytes and osteoblast are both of mesoderm origin and share many gene expression characteristics during differentiation even though their phenotype differ markedly. Mature adipocytes and osteoblast express and secrete several common factors that underline a close relationship between them [21], the potential mechanism of this relation is through the differentiation transcription factors, runt-related transcription factor 2 (Runx2) for osteoblast and the peroxisome poliferator-activated receptor gamma (PPARg) for adipocytes [24].

In summary, in the context of insulin resistance, osteocalcin treatment has demonstrated to increase adiponectin secretion, to promote the expression of the anti-inflammatory cytokine *IL10*, and to decrease the secretion of TNFα and IL6.

Pancreatic function

Diabetes in all its forms is characterized by loss of glycemic control developed partly from pancreatic ß-cell destruction. In type 1 diabetes, this loss is autoimmune-mediated and in type 2 diabetes is caused by glucotoxicity, lipotoxicity, and increased production of pro-inflammatory cytokines [12].

Continuous and intermittent administration of ucOCN has demonstrated to lowered blood glucose levels, increased ß-cell mass, insulin secretion, and insulin sensitivity [10,27,29]. Ferron et al. had found that both deliveries forms have similar effects [10]. In wild-type mice, continuous infusion of high doses of ucOCN (3–30 ng/h) reduced fat mass and improved insulin sensitivity, while, low doses (0.3–3 ng/h) increased ß-cell proliferation and insulin secretion. Furthermore, intermittent administration of ucOCN with daily injections increased efficiently insulin secretion and glucose tolerance with a high dose (30 ng/g/day) and was more efficient in the improvement of insulin sensitivity in a low dose (3 ng/g/day) [10,27].

Long-term effects of ucOCN tested by the oral administration of 3 ng/g of ucOCN three times a week, for 13 weeks in mice fed with normal diet showed to increase ß-cell area, improved ß-cell proliferation, glucose tolerance, and insulin secretion [29]. In the small intestine, ucOCN concentrations remain constant among 3 and 24 h, suggesting that its effects continue for a period of time. The mechanisms of ucOCN orally administered could be mediated by the stimulation of glucagon-like peptide 1 (GLP-1) secretion by L-cells of the small intestine [29].

The therapeutic potential of ucOCN has been examined in mice fed with HFD and in mice fed with a high sucrose diet. Osteocalcin was administrated orally at a dose of 10 ng/g, three times a week, for 13 weeks and showed to reduce blood glucose and to improve blood glucose clearance [29]. In addition, daily injections of ucOCN proved to prevent liver steatosis in mice fed with HFD. ucOCN has demonstrated to be able to decrease blood triglycerides levels and fat accumulation in wild type and obese mice, the above may be positive in the improvement of insulin sensitivity in muscle, WAT, and other insulin target tissues [10].

ß-cell mass is regulated by an equilibrium of several process among neogenesis, hypertrophy or atrophy, cell differentiation, cell proliferation, and cell death [30]. Mostly, ß-cell mass increase occurs during late embryonic development to 30 days post birth in mouse,after this, it abruptly decreases. Cell proliferation is the main process for the increase of ß-cell mass, this process involves diverse intracellular factors, which include cell-cycle regulators such as cyclin D1 (Ccnd1), cyclin D2 (Ccnd2), and

cyclin-dependent kinase 4 (Cdk4) [31]. In adults, ß-cell proliferation rate is in a range between 0 and 1.2%, nevertheless, during pregnancy or dietary challenge this low rate can be increased. Osteocalcin has proved to have an important role in the regulation of ß-cell mass via Gprc6a receptor during mice development and adulthood, moreover perinatal ß-cell proliferation peak coincides with increase in osteocalcin expression [30,31].

Previous studies have demonstrated that osteocalcin enhances expression of insulin genes (*INS1* and *INS2*) and cell-cycle transition proteins such as Ccnd1, Ccnd2, and Cdk4 in mouse islets or cultured ß-cell lines. In Gprc6aPdx1$^{-/-}$mice, a model of Gprc6a specific inactivation in the ß-cell linage, ß-cell mass was significantly reduced and *Ccnd1* expression decreased during embryonic development and adulthood. In developing islets of Gprc6aPdx1$^{-/-}$mice, no measurable differences were found between the expression of differentiation markers (*PDX1*, *NKX6.1*, *NKX2.2*, or *ISL1*) comparing with their littermates. This suggests that osteocalcin could contribute to the regulation of ß-cell proliferation in a differentiation-independent form [31]. Continuous administration of osteocalcin for 4 weeks has demonstrated to increase ß-cell proliferation as well as 16 weeks of daily injections [10].

In human islets in vitro, treatment with 1.0 ng/mL of ucOCN increased ß-cell mass percentage. Pancreatic human cells were transplanted to immunodeficient NOD mice and received ucOCN treatment (4.5 ng/h). The islet grafts removed showed that 20% of the insulin-positive cells were in proliferation, no ß-cell exhaustion or functional failure signs were found in 30 days of monitoring [12]. Moreover, alignment analyses have shown that osteocalcin gene is well conserved between different species. Human osteocalcin exhibits a similarity of 93.9% to bovine osteocalcin and of 87.8% to pig osteocalcin [32], in this way, the function of Gprc6a and osteocalcin could be preserved in humans [31].

Osteocalcin has demonstrated to have a key role in pancreatic function. Osteocalcin effects include improvement of insulin expression, secretion, and sensitivity, ß-cell proliferation, stimulation of GLP-1 secretion, decrease blood triglycerides levels, and prevention of liver steatosis. Moreover, osteocalcin effects have been proved to be conserved in human cells.

Oxidative stress relation

In diabetes, glucose toxicity caused by chronic hyperglycemia leads to progressive ß-cell dysfunction and ß-cell loss by apoptosis [33]. ß-cell is vulnerable to damage caused by reactive oxygen species (ROS) due to their low antioxidant mechanisms and its inefficiency repairing oxidative DNA damage. Osteocalcin has been shown to regulate gene expression to enhance protective mechanisms against cellular stress [34].

Thioredoxin-interacting protein (TXNIP), a protein containing 391 amino acid residues, that is encoded on human chromosome 1 and mouse chromosome 3 [35] binds to and inhibits thioredoxin, promoting oxidative stress [36]. *TXNIP* induces cell-cycle arrest at the G0/G1 phase, exerts antiproliferative effects and its overexpression rendered fibroblast, and cardiomyocytes more susceptible to apoptosis [33]. Also, it has been proposed that *TXNIP* is an important regulator of osteocalcin production and carboxylation status [37].

TXNIP has been considered an early response gene with a rapid transcriptional regulation [36]. Microarray studies in human isolated islets have demonstrated that in high glucose concentrations *TXNIP* expression increase dramatically (tenfold) [35,36]. It has been proposed that glucose stimulates *TXNIP* transcription through a carbohydrate response element identified ChoRE-400 bp of the human TXNIP promoter that is conserved in mouse and rat and that is not only necessary, but sufficient to confer glucose responsiveness [33,36]. In islets cultured in high glucose concentrations for 48 h osteocalcin treatment decreased *TXNIP* expression [34].

Increased *TXNIP* expression has been associated with decreased expression of genes related with insulin expression like the transcription factor MafA [34]. Other analysis had revealed that TXNIP protein levels are elevated in isolated islets from obese, insulin-resistant, and diabetic *ob/ob* mice compared with islets from lean normoglycemic mice. TXNIP increase produce an equal rise of cleaved caspase-3 levels suggesting increased apoptosis [35], the above was also observed in INS1 ß-cells exposed to high glucose concentrations (25 mmol/l) for 24 h [33].

In type 1 and type 2 diabetes, the major form of pancreatic ß-cell loss is apoptosis [36]. In mitochondria-mediated apoptosis, a disequilibrium in proapoptotic Bax and antiapoptotic Bcl-2 occur with a disruption of the mitochondrial membrane potential, this results in release of cytochrome C into the cytosol and caspase-9 activation. In transfected cells INS-TXNIP or INS-LacZ (control), INS-TXNIP cells have been shown to release cytochrome C into the cytosol, contrary to control cells where cytochrome C remains localized to the mitochondria. *TXNIP* overexpression led to a profoundly increase in ß-cell apoptosis. In high glucose conditions, INS1E cells have higher caspase activity, while, osteocalcin treatment has been shown to reduced caspase activity at 48 and 72 h [34].

In addition, *TXNIP* overexpression made INS1 ß-cell more susceptible to oxidative stress induced by H_2O_2. Cells overexpressing *TXNIP* (INS-TXNIP) exposed to H_2O_2 showed 26% apoptotic cells compared with 13.6% in control cells (INS-LacZ) [36]. Also, in rat isolated islets, H_2O_2 content was higher in high glucose treated cells compared to cells in normal conditions. Osteocalcin

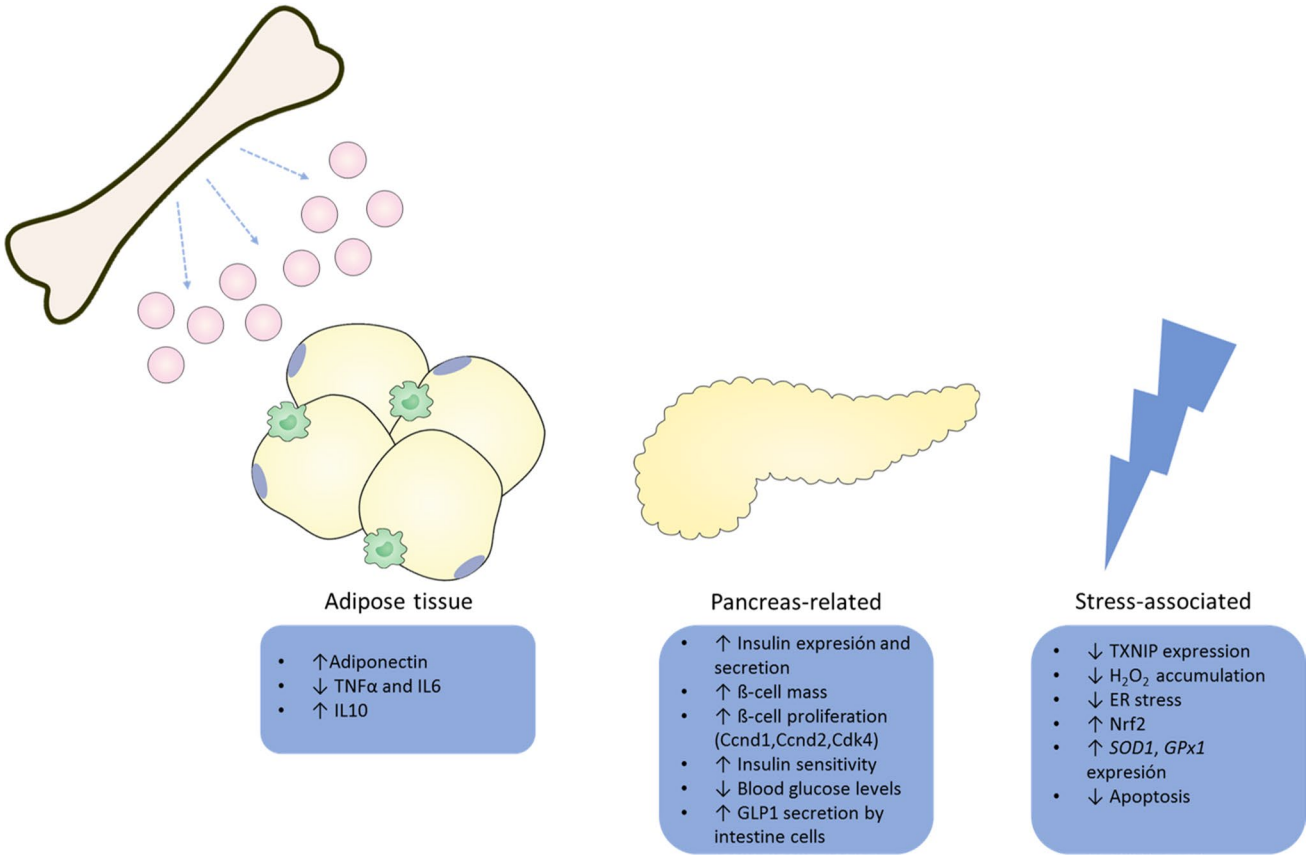

Fig. 2 Integrative view of osteocalcin functions in diabetes. Osteocalcin has demonstrated to have an integrative function in diabetes. Osteocalcin acts in various tissues and is involved in the response to different metabolic disturbances

has demonstrated to significantly reduce glucose-induced H_2O_2 accumulation at 48 h with a further reduction at 72 h [34].

On the other hand, endoplasmic reticulum (ER) stress plays a key role triggering insulin resistance in obesity [38]. ER stress pathway involves depletion of calcium stores in ER, accumulation of unfolded proteins, and upregulation of ER chaperones such as BiP. Persistent ER stress leads to activation of apoptosis cascade which produces upregulation of transcription factors such as ChOP and activation of caspase-12 [33].

Osteocalcin reverse insulin resistance partially caused by ER stress. In cells exposed for 4 h to the ER stress inducer tunicamycin (5 µg/mL), osteocalcin was able to attenuate ER stress and restore insulin sensitivity via PI3K/Akt/NF-kB signaling pathway in 3T3-L1 adipocytes, Fao liver cells, and L6 muscle cells. When cells exposed to tunicamycin, were additionally treated with osteocalcin, IRS-1 tyrosine and Akt Ser-473 phosphorylation were significantly enhanced. The use of the inhibitors wortmannin (a PI3K inhibitor), Akti-1/2 (an Akt inhibitor) and pyrrolidine dithiocarbamate (a NF-kB inhibitor) nullified the protective effect of osteocalcin, this allowed the identification of PI3K/Akt/NF-kB as a signaling pathway involved in this process [38].

In mice, an intervention with HFD for 4 weeks induces ER stress in liver, adipose tissue, and skeletal muscle, while osteocalcin treatment showed to reduce ER stress. In *ob/ob* mice, treatment with osteocalcin for 5 days reduced blood glucose, reversed ER stress, and improved insulin signaling [38]. Furthermore, ucOCN has proved to reverse ER stress and restore insulin signaling via PI3K/AKT/NF-KB signaling pathway in human umbilical vein endothelial cells (HUVECs) [39]. HFD induced an increase in hepatic malondialdehyde (MDA) and 8-isoprostane-prostaglandin F2α (8-iso-PGF2α) levels, which are products of lipid peroxidation, as well as, a higher ratio of GSSG/GSH, which is an indicator of redox balance, these elevations had been proved to be attenuated by 12 weeks osteocalcin treatment [40].

Besides, in mice fed with HFD, treatment with osteocalcin increased the level of nuclear factor-E2-related factor-2 (Nrf2) in the nucleus, Nrf2 is a key regulator of the expression of genes encoding enzymes of the antioxidant system, consequently osteocalcin also increased the expression of catalase, *SOD-1*, and *GPx-1* in liver [40].

Osteocalcin has demonstrated to reduce *TXNIP* expression, caspase activity, H_2O_2 accumulation, to reverse ER stress, and to increase Nrf2 levels, and the expression of antioxidant enzymes. Considering that oxidative stress is associated with ß-cell apoptosis, diabetes, and development of chronic complications, osteocalcin may have a beneficial effect in pancreatic ß-cells preventing its progressive failure and the damage of other tissues involved in diabetes pathogenesis [33,34].

In conclusion, osteocalcin endocrine functions have been implicated in many metabolic processes and when pieces are placed together, a big framework appears where osteocalcin could module different aspects of diabetes (Fig. 2).

Osteocalcin has revealed to participate in different stages of diabetes development. Moreover, osteocalcin has proved to have an important role in metabolic, inflammatory, and stress-associated disturbances that are the hallmark of diabetes pathology. Finally, more investigation is necessary to evaluate the potential use of osteocalcin as an adjuvant treatment in insulin resistance and in diabetes.

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Author contributions M. F. D. D. wrote the manuscript. J. D. R. C. and S. S. E. critically revised the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that there is no duality of interest associated with this manuscript.

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