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ORIGINAL RESEARCH

Bone-Derived Factors: A New Gateway to Regulate Glycemia

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Abstract Type 2 diabetes mellitus (T2DM) and osteoporosis are two major disorders which prevalence increases with aging and is predicted to worsen in the coming years. Preclinical investigations suggest common mechanisms implicated in the pathogenesis of both disorders. Recent evidence has established that there is a clear link between glucose and bone metabolism. The emergence of bone as an endocrine regulator through FGF23 and osteocalcin has led to the re-evaluation of the role of bone cells and bone-derived factors in the development of metabolic diseases such as T2DM. The development of bone morphogenetic proteins, fibroblast growth factor 23, and osteoprotegerin-deficient mice has allowed to elucidate their role in bone homeostasis, as well as revealed their potential important function in glucose homeostasis. This review proposes emerging perspectives for several bone-derived factors that may regulate glycemia through the activation or inhibition of bone remodeling or directly by regulating function of key organs such as pancreatic beta cell proliferation, insulin expression and secretion, storage and release of glucose from the liver, skeletal muscle contraction, and browning of the adipose tissue. Connections between organs including bone-derived factors should further be explored to understand the pathophysiology of glucose metabolism and diabetes.

Keywords Osteokine · Glucose · Insulin · Browning · Steatosis · Beta-cell

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Introduction

The skeleton has been demonstrated to be determinant to preserve the mechanical integrity of the organism and to regulate calcium and phosphorus homeostasis. The high bone remodeling activity and vascularization of the skeleton also suggest that the bone tissue by its surface can have additional contribution to physiology of the whole organism, such as in glucose homeostasis [1]. Type 2 diabetes mellitus (T2DM) and osteoporosis are two major chronic disorders which prevalence increases with aging and is predicted to worsen in the coming years [2]. As an example, the prevalence of diabetes is expected to increase by 55% in the next 20 years, rising from 382 million people worldwide in 2013 to 592 million by 2035. The estimated number of osteoporotic hip fractures worldwide will also rise from 1.66 million in 1990 to 6.26 million in 2050 [3]. Both osteoporosis and diabetes are associated with an increased risk of fragility fractures, resulting from alterations of bone quality as well as a propensity to falls, associated with a loss of muscle function [4], providing the clinical characteristics of diabetoporosis (or diabetes in osteoporosis). Recently, a clear link between glucose metabolism and bone has been highlighted [5, 6]. More specifically, in vitro investigation demonstrated that high bone resorption and low bone formation in type 2 diabetic patients can be explained by a direct up-regulation of sclerostin (a major Wnt inhibitor, specifically expressed in osteocyte) by high glucose levels [7]. However, other mechanisms have been mentioned to explain the decline of bone strength: a decrease in the neovascularization, an increase in the mesenchymal stem differentiation into adipocyte rather than into osteoblasts, and accumulation of glycation end products (AGEs) decreasing the mechanical properties of the matrix [8, 9]. Hence, the exact

pathophysiology of bone fragility in T2DM patients remains to be determined.

More recently, based on the cardinal rule of physiology that a regulated organ takes back to a regulating one to limit its influence, bone has been shown to regulate the whole body glucose homeostasis. Bone is known as an insulin-regulated tissue [10], but importantly, existence of feedback has emerged, with osteocalcin, an osteoblast-derived osteokine, reported to increase insulin release from beta pancreatic cells and indirectly to increase insulin action through enhanced release of adiponectin from adipose tissue [11, 12]. Hence, bone might contribute to the regulation of glucose homeostasis and an impairment of this control loop can favor diabetes occurrence. The fact that bone remodeling occurs daily, in multiple locations and in an organ covering a very large surface area, suggests that bone has a high energy demand which needs to be tightly regulated. Therefore, bone may needs more than one osteokine to regulate glucose resources. Few analyses have already indicated that bone is the fourth organ after adipose tissue, liver, and skeletal muscle to store glucose [13, 14]. Altogether, these data indicate a need to study how the skeleton can regulate energy metabolism, i.e., glucose homeostasis. Glucose regulation by bone-derived factors will particularly be reviewed here.

Glucose Consumption by Bone Cells Contributes to Glucose Homeostasis

Bone remodeling activity performed by osteoblasts—the bone forming cells—and osteoclasts—the bone resorbing cells—and their coordination by osteocytes, the end-product of osteoblast differentiation requires an amount of energy which can be important by taking into account the number of cells in the skeleton. Osteoblast, osteocyte, and osteoclast exhibit well-developed Golgi apparatus, endoplasmic reticulum, and mitochondrial activity [15]. Interestingly, cellular glucose metabolism has been shown to regulate osteoblast biology [16], so osteoblast differentiation, collagen synthesis, and bone formation activity are tributary to the amount of energy which is available. More precisely, intracellular entry of glucose, regulated by Glut1 glucose transporter, promotes RUNX2 transcriptional factor and the accumulation of glucose into osteoblasts [14]. By using the euglycemic hyperinsulinemic clamp, we confirm data from Karsenty laboratory, showing that bone takes up one-fifth of the quantity of glucose taken by skeletal muscle (80 ng/mg tissue/min), the tissue taking up the majority of glucose in the mouse after the brown adipose tissue (290 ng/mg tissue/min) [14].

Intracellular machinery yield rate which determine the amount of glucose which will be consumed can change in response to different treatments. For example, rats receiving PTH roughly increased structure and enzymatic activity of endoplasmic reticulum mitochondria and Golgi apparatus of osteoblast and osteocyte without affecting those of osteoclast [17]. In accordance, a randomized clinical trial showed that PTH increased bone formation, i.e., osteocalcin, and decreased blood glucose without influencing insulin secretion or resistance [18]. Thus, the hypothesis that PTH contributes to glucose homeostasis through the bone tissue himself remains possible. A preclinical study recently highlighted that intermittent PTH reduces glycemia by increasing aerobic osteoblast glycolysis via IGF signaling [19].

In contrast, additional sex combs-like (ASXL2), an enhancer of trithorax and polycomb family protein which interacts with PPARγ, promotes osteoclast mitochondrial biogenesis, i.e., glucose consumption, through PGC-1β independently of the c-Fos-NFATc1 pathway classically required for bone resorption activity. In accordance, authors demonstrated that ASXL2-deficient mice exhibit high glucose levels and are glucose intolerant [20]. In vitro, in basal condition, investigation of 2-[U-^{14}C] deoxyglucose (2-DG) uptake illustrates that either osteoblast or osteoclast consumes around 20 µmol/g protein/min of glucose each compared to 60 µmol/g protein/min for myoblast, arguing that both formation and resorption cells are able to consume a substantial amount of glucose.

Since 10 years, a new bone endocrine function has emerged: the production of osteocalcin for the control of glucose homeostasis. In this model, osteocalcin modulates three other hormones: Insulin secreted by beta cells of the pancreas [21]; adiponectin secreted by adipocytes, known to reduce insulin resistance [12, 22]; and testosterone synthesized by Leydig cells and favoring fertility [23] (Fig. 1). Hence, we will review in the next paragraph whether, in addition to osteocalcin, other bone-derived factors could be able to modulate energy metabolism.

Glucose Regulation by Bone-Derived Factors

Osteocalcin

Osteocalcin also named bone gamma-carboxyglutamic acid-containing protein (BGLAP) is a non-collagenous protein secreted by osteoblast/osteocyte. Osteocalcin plays a role in the mineralization process by having a high affinity with calcium. In clinical practice, osteocalcin is used as a marker of bone formation and more broadly of bone remodeling. Osteocalcin can also be undercarboxylated (unOC), by the acidification of the matrix performed by osteoclast, exhibiting glutamic acid instead of gamma-carboxyglutamic acid. This form is released into the

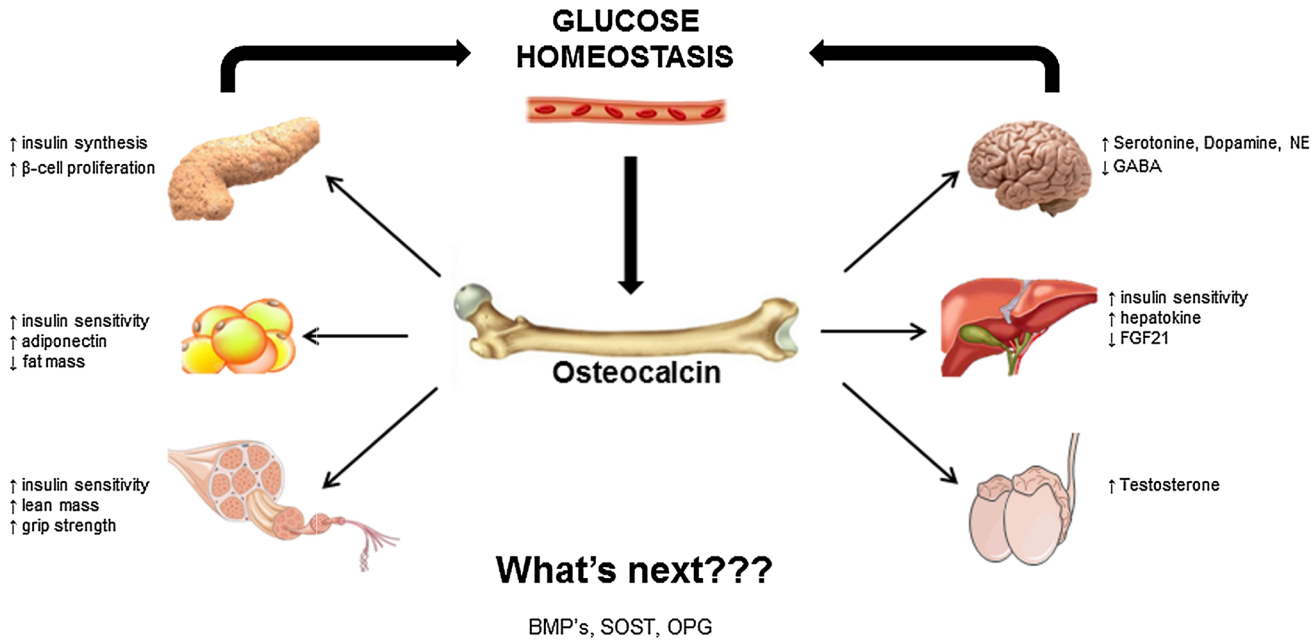

Fig. 1 Bone-derived factor, control of glucose metabolism. Osteocalcin exhibits an important endocrine function by targeting multiple tissues: pancreas, adipose tissue, skeletal muscle, brain, and liver testis. However, osteocalcin might not be the only factor produced by bone cells (osteoclast, osteoblast, and/or osteocyte) involved in the regulation of glucose homeostasis

bloodstream and has been considered to be the bioactive form able to regulate energy metabolism. Historically, metabolic function of osteocalcin has been investigated by characterizing the phenotype of the enterococcal surface protein (Esp)-knockout mouse ($Esp^{-/-}$). Esp gene encodes an osteotesticular protein tyrosine phosphatase (OST-PTP) in osteoblast, a tyrosine phosphatase which stimulates the carboxylation of osteocalcin. Hence, $Esp^{-/-}$ mice exhibit an increased level of unOC, as well as increased insulin and adiponectin expression, increased insulin secretion and sensitivity, increased lean, and decreased fat mass and triglyceride levels. In contrast, osteocalcin-deficient mice, which have low unOC circulating levels, are fat, insulin resistant, glucose intolerant, and hyperlipidemic [21]. The proof of concept that unOC is able to impact pancreatic beta cell, adipocyte, or myocyte has been demonstrated by co-culturing $Esp^{-/-}$ osteoblast with primary beta cell or adipocyte of WT [12, 21] and was confirmed later on subsequently with the treatment of WT mice with osteocalcin [24] and with the phenotypic characterization of the GPRC6A 'osteocalcin receptors'- deficient mice [25, 26]. Several studies also show that both injection and oral administration of unOC can abrogate the deleterious effects of high-fat diet on glucose metabolism [11, 27].

In addition to the direct effect of unOC on insulin secretion, it has been shown that unOC increases insulin secretion indirectly through an increased secretion of glucagon-like peptide-1 (GLP1) from intestinal endocrine cells [27].

The effects of unOC on skeletal muscle have been suggested with the demonstration that unOC increases the fusion rate of the C2C12 lining cells in vitro [28, 29] and improves significantly grip strength in vivo by increasing muscle volume [30, 31]. In addition, unOC increases insulin signaling in muscle, contributing to glucose metabolism.

Transfer to humans has also been largely investigated. Several cross-sectional studies highlighted the association between osteocalcin serum level and blood glucose, and HbA1c and metabolic syndrome [32]. A proof of concept study using surgical resection of osteoma osteoid showed a direct effect of osteocalcin on glucose serum level [33]. In addition, the fact that patients with a mutation of GPRC6A receptor, the receptor of osteocalcin, do have an impaired glucose metabolism and a low sperm count [34] also sustains relevance of osteocalcin physiology in humans. Nevertheless, direct evidence of the role of osteocalcin in humans is scarce and large-scale prospective studies are needed. Several limitations need to be mentioned. Caution must be taken particularly because murine and human osteocalcins are not the same size and differ in some amino acids [35]. In humans, majorities of the studies show association between total osteocalcin and glucose metabolism (such as plasma glucose, fasting insulin, and resistance) rather than with unOC. Another reason is that it is not completely clarified whether the active form is the fully unOC or only the partially unOC form. In the same line, because research and commercial assays for

measuring unOC are not standardized, it is difficult to compare results between studies, and this could influence the interpretation of the results. The specificity of osteocalcin to the bone tissue is now also questioned since the two forms of osteocalcin are also expressed in adipose tissue [36]. Osteocalcin is maximally expressed in preadipocytes and expression decreased during adipocyte differentiation [36]. Osteocalcin has also been suggested to be produced in the brain and to possibly function as a neuropeptide [37]. In this regard, further studies are needed to clarify the precise regulation of osteocalcin released from adipose and/or brain in different physiological contexts of obesity, metabolic syndrome, and T2DM. While osteocalcin replacement in osteocalcin-null mice can reverse the glucose intolerance and correct glucose levels, it could not restore insulin sensitivity, indicating that other bone-derived factors may also mediate insulin action [38]. More recent investigation on NPY signaling in early osteoblasts also argues for a control of glucose homeostasis by other osteokines than unOC [39].

Major factors controlling both glucose homeostasis and osteoblast/osteocyte differentiation are the bone morphogenetic proteins (BMPs) [40].

BMPs

BMPs are members of the transforming growth factor (TGF-β) superfamily, originally discovered for their ability to induce bone and cartilage formation [41]. BMPs are now known to regulate embryonic development of multiple tissues by the phosphorylation of the intracellular BMP effector proteins SMADs [42]. They have been shown to be crucial in metabolic pathologies such as T2DM and obesity by regulating inflammation, glycemia, and energy metabolism. We will particularly focus on BMP2, BMP4, and BMP7 already known to impact hepatic fibrosis, endocrine cell differentiation of the pancreas, and browning of the adipose tissue.

Interestingly, BMPs and their respective receptor are not systematically expressed in the same tissue suggesting an important endocrine function of BMPs. For example, BMP7 receptor is expressed in hepatocyte and its activation has an anti-apoptotic and anti-inflammatory effect improving liver regeneration; however, BMP7 is not expressed in liver [43], but is mainly expressed by the kidney, pulmonary artery, cartilage, and bone.

Hence, as for osteocalcin, the feedback loop could also exist for BMPs. Insulin signaling in osteoblast/osteocyte, decreased OPG/RANKL ratio, and during the initial phase of demineralization, BMPs initially embedded in the matrix can be released into the bloodstream (Fig. 2). This mechanism has already been suggested to explain the coupling between bone resorption and bone formation and is probably also involved in the coupling between bone, pancreas, and adipose tissue (Fig. 2).

Effects of BMPs in Pancreatic Beta Cell

In the pancreas, ablation of BMP receptor (*BMPr1a*) in beta cells leads to glucose intolerance, decreased expression of genes involved in glucose sensing and metabolism, and decreased insulin production and secretion [44, 45]. On the contrary, overexpression of BMP4 improves glucose tolerance and insulin secretion as well as markers of islet function [44]. However, the interaction between BMP4 and insulin secretion during the development of diabetes is not so clear. It was reported that glucose-induced insulin secretion was significantly impaired in rodent and human islets pre-treated with BMP4, and inhibition of BMP activity resulted in enhanced insulin release, in part through an increased proliferation of beta cells [46]. On the contrary, recombinant human BMP3 in INS-1 potently increased insulin expression and protein [47]. The various effects among the BMPs on beta cell induce different phosphorylations of the SMAD signaling pathway, for example, BMP3 signals through phospho-SMAD2/3 similar to TGFβs, whereas BMP4 through phospho-SMAD1/5/8. Discordant data reported in the literature may also come from the differential effects of BMPs induced during developmental and adult lives. The specific contribution of BMPs secreted locally compared to circulating levels of BMPs arising from other tissues can also contribute to discrepancies observed between studies.

The complexity of BMPs effects on glucose homeostasis may come from their ability to target several tissues, as it is the case for BMP9 and BMP7. BMP9 targets both the liver and pancreas, respectively, by inhibiting hepatocyte glucose production, activating key enzyme of lipid metabolism (malic enzyme and fatty acid synthase), and stimulating insulin secretion by pancreatic beta cell in normal and diabetic mice [48]. In addition to its role in liver fibrosis (see above), BMP7 has been reported to improve glucose homeostasis by increasing insulin production through the conversion of pancreatic exocrine tissue (98% of the organ) to an endocrine one, expressing beta cell master genes [49].

Effects of BMPs on Browning of the Adipose Tissue and Consequences in Energy Metabolism

Among all BMPs, involvement of BMP-2, BMP4, BMP6, and BMP7 has been well described in the differentiation of the mesenchymal stem cell into the adipogenic lineage [50]. In recent findings, the evidence of a role for BMPs on adipose tissue comes from studies of the knockout models. BMP7-deficient mice exhibit a reduction in brown adipose

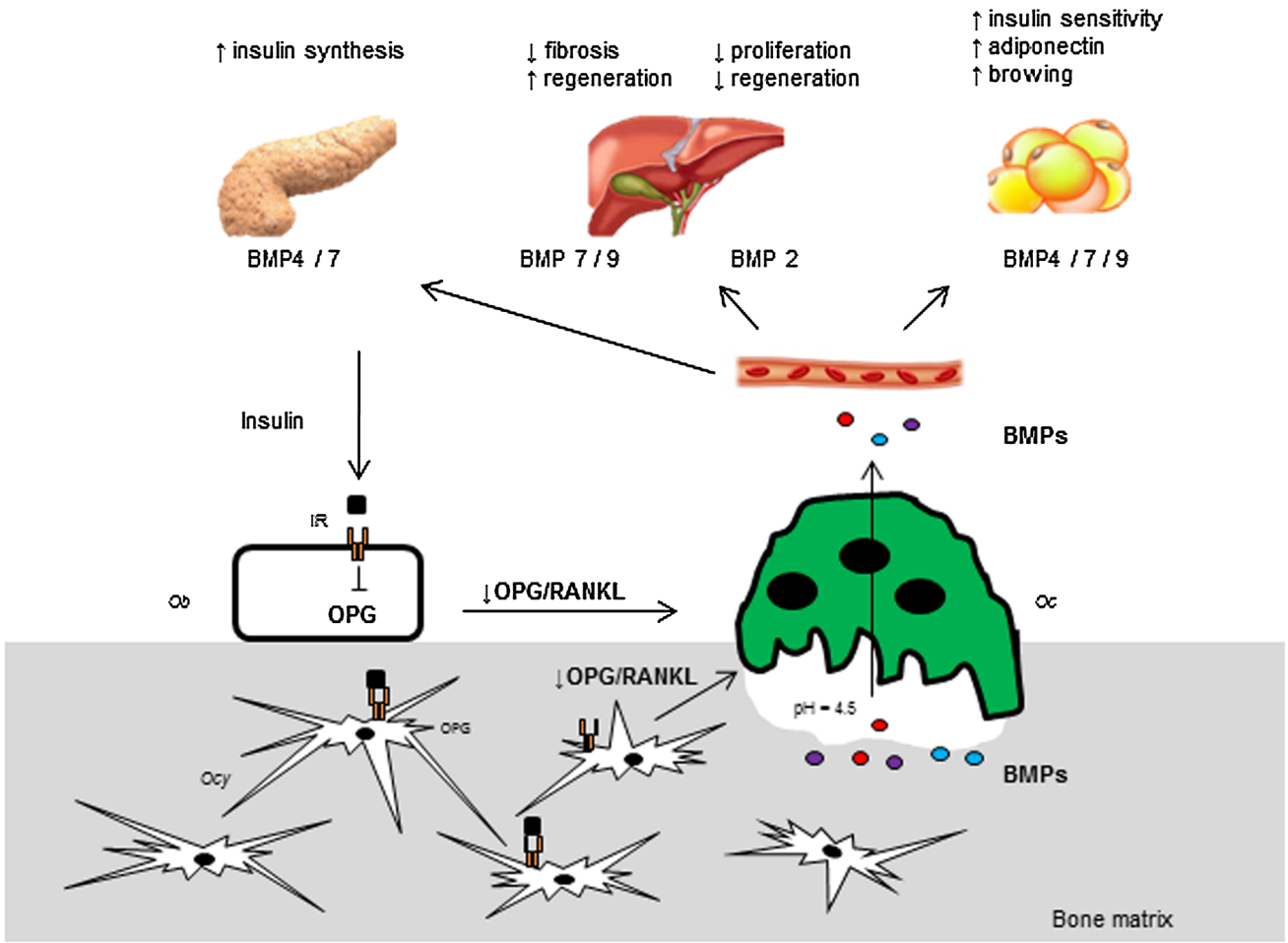

Fig. 2 Potential effects of BMPs released by the bone tissue on glucose homeostasis. BMP2, BMP4, BMP7, and BMP9 are all synthesized by the bone tissue and all regulate metabolic tissues such as the pancreas, liver, and adipose tissue. Insulin signaling in osteoblasts (Ob)/osteocytes (Ocy) decreases the expression of OPG, by decreasing OPG/RANKL ratio and increasing bone resorption. Osteoclastic (Oc) activity releases bone proteins embedded in the matrix such as bone morphogenetic proteins (BMPs) into the bloodstream. BMPs secondarily exert an action on key organs involved in glucose metabolism pancreas, liver, and adipose tissue

tissue (BAT), without any changes in white adipose tissue (WAT) [51]. Morphologically, WAT and BAT differ by their droplet size and abundance. WAT stores triglycerides in a single large lipid droplet and contains few mitochondria, while BAT shows many small lipid droplets and a lot of mitochondria. BAT by expressing uncoupling protein 1 (UCP1) increases cellular respiration from ATP production and burns much more lipid and glucose than WAT. Hence, overexpression of UCP1 protects mice from diet induced obesity [52]. In particular, BMP7 stimulates the expression of PR domain containing 16 (PRDM16), a factor responsible for triggering commitment of mesenchymal stem cell into BAT rather than to WAT. BMP7 and BMP8B also act on mature BAT to promote thermogenesis by increasing UCP1 and lipolysis through phosphorylation of P38-MAPK. Unlike BMP-8B, BMP7 is not expressed in mature BAT, suggesting that it does not work in an autocrine or paracrine manner, but rather as an endocrine factor as seen for the liver [53]. Overexpression of BMP4 in WAT resulted in decreased fat mass with reduced adipocyte size coupled with an increased number of brown or beige adipocytes and an increase in insulin sensitivity [54].

On the contrary, BMP2 is expressed in adipose tissue and has been shown in vitro to promote adipogenesis into WAT [55]. Hence, BMP2 KO mice exhibit a reduction in white fat mass. However, conflicting data remain concerning BMP4 signaling depending on the cell lines investigated [56].

In summary, in addition to their major contribution to skeletal remodeling, BMPs also play a key role in glucose homeostasis. However, several discordances remain and additional experiments with tissue-specific strategies will be required to better characterize the tissue specificity of BMPs as well as the contribution of bone to circulating levels of BMPs.

OPG

Osteoprotegerin (OPG) is a soluble glycoprotein that belongs to the tumor necrosis factor (TNF) receptor superfamily. In the bone tissue, it is secreted by osteoblast and acts as a decoy soluble receptor for the receptor activator of nuclear factor kB (NF-kB) ligand (RANKL), thus preventing RANKL from binding to its receptor on osteoclasts, thereby inhibiting osteoclastogenesis. Denosumab, a human monoclonal antibody against RANKL, has been used for nearly 5 years to treat osteoporosis and appears to be the most powerful inhibitor of bone remodeling [57]. It is now known that RANK and RANKL are both expressed in other tissues such as liver, pancreatic beta cell, skeletal muscle and in several tumors. Hence, activation of RANK has been reported to be involved in several diseases impairing glucose homeostasis. In a mouse model of T2DM, inhibition of RANKL signaling improves hepatic insulin sensitivity and normalizes plasma glucose concentration [58]. In skeletal muscle, inhibition of RANKL by OPG-immunoglobulin fragment complex (OPG-Fc) treatment increases skeletal muscle force from dystrophic mice [59]. OPG-Fc specifically reduces muscle inflammation, i.e., neutrophil and macrophages cells numbers and muscle damage, evaluated by hematoxylin and eosin staining. Such investigations need to be confirmed since these effects are observed only in extensor digitorum longus of dystrophic mdx mice and not in wild-type mice. However, such data argue for an improvement of glucose homeostasis by OPG-Fc treatment [59].

In a model of inflammation by microbial invasion, OPG production by beta cell is increased, which inhibits insulin secretion. In accordance, in vitro, OPG treatment of MIN6 pancreatic beta cell lines decreased insulin release following glucose stimulation. Hence, OPG would locally act as a negative feedback, preventing exhaustion of beta cell endocrine function [60].

In women with diabetes who were not receiving any anti-diabetic medication, RANKL neutralizing antibody not only reduced fractures but also significantly decreased fasting serum glucose [61]. However, associations between the levels of OPG and/or RANKL and parameters of glucose homeostasis such as HOMA, insulin sensitivity, and fasting glucose are producing conflicting results [62–64].

Hence, further study is needed to elucidate several points: (1) the direct effect of OPG/RANKL on each tissue involved in the regulation of glucose homeostasis; (2) the skeletal contribution versus non-skeletal of OPG and/or RANKL to circulating levels; (3) the role of RANKL/OPG on decarboxylation of osteocalcin, i.e., metabolic active form of osteocalcin, an indirect mechanism for RANKL/OPG to control glycemia.

To date, a real clinical trial with denosumab is needed with glucose homeostasis as a primary endpoint.

FGF23

In the bone, the most abundant cell is osteocyte also described as the chief of orchestra of bone modeling and remodeling. The first discovered hormone expressed by bone and mostly by osteocytes was FGF23. FGF23 is well characterized for its important role in regulating serum phosphate levels. Surprisingly, in addition to their expected altered phospho-calcic metabolism, FGF23-deficient mice exhibit hypoglycemia as well as increased insulin sensitivity [65]. Interestingly, clinical studies also confirm an association between FGF23 and energy metabolism. In two independent cohorts, 'Osteoporotic Fractures in Men Study' and 'Vasculature Uppsala Seniors study,' an association between FGF23, dyslipidemia, and fat mass has been reported [66]. Hence, FGF23 levels were higher in subjects with metabolic syndrome compared to healthy patients [66]. However, the precise role of FGF23 in energy metabolism is not well understood, and precision must be given on its direct and/or indirect action. Two reviews reported that FGF23 pathway could be involved in energy metabolism, and this could be mediated by bone [67, 68]. FGF23 would inhibit enterococcal surface protein (see above) and decreased bone resorption, decreasing the release of unOC.

SOST

As described above, low bone turnover in T2DM patients can be explained by an up-regulation of sclerostin accompanied by an uncoupling remodeling (decrease in bone formation and increase in bone resorption) [7]. Type 2 diabetic patients have increased plasma sclerostin associated with BMI, abdominal fat, higher fasting plasma glucose, and blood insulin sensitivity, suggesting that sclerostin may be implicated in diabetes pathogenesis [69, 70]. These associations led to the question whether circulating levels of sclerostin have a biological effect? In that regard, serum sclerostin is associated with vascular calcification in postmenopausal women [71], T2DM [72], and chronic kidney diseases and hemodialysis patients [73]. More recently, preliminary data from MINOS cohort indicated in men that the highest quartile of sclerostin was associated with the highest odds ratio (OR 2.40 [95% CI 1.33–4.41] $p < 0.005$) of metabolic syndrome (defined by a glycemia >5.6 mmol/l, arterial pressure >130/85 mmHg, triglycerides >1.7 mmol/l; HDL-cholesterol <1.03 mmol/l) compared to the lowest quartile [74]. The Wnt signaling pathway is active in key organs of glucose homeostasis such as pancreas, adipose tissue, liver, and skeletal muscle [75–78]. Hence, all the regulators of this signaling pathway can exert an effect on glucose homeostasis. For example, in a preclinical study, Bmp/Wnt signaling has been shown to

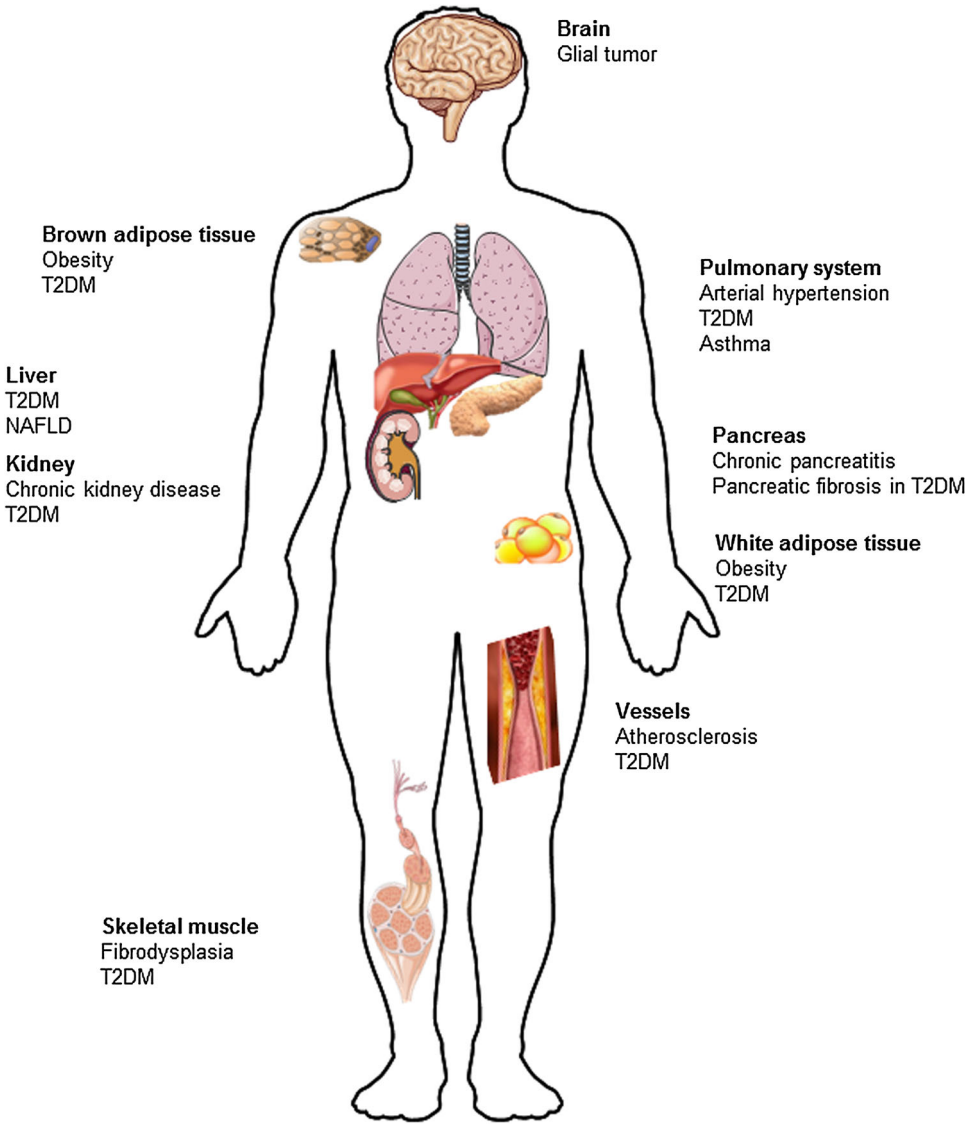

Fig. 3 Soft tissue calcification and association with human diseases impacting glucose homeostasis. Bone matrix proteins are expressed in different organs, particularly during inflammation or fibrosis occurring in several diseases [83, 85–91]. These tissues expressing bone matrix proteins are involved directly or indirectly in the regulation of glucose homeostasis, leading to the idea that 'extra skeletal tissues' contribute to the regulation of energy metabolism. Type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD). As an example, pancreatic calcification is seen on radiographs in about 30–50% of patients with chronic pancreatitis in adults and increases the risk of secondary diabetes [92]. However, the specific role of bone matrix protein in such observation needs to be further investigated

be important in islet development, function, and insulin production and secretion [79]. More recently, the loss of expression of Wnt inhibitor (Sostdc-1) in mice has been shown to enhance insulin secretion and glucose homeostasis. These studies provide insight into modulators of BMP/Wnt pathway in the endocrine pancreas and reveal potential avenues for Wnt inhibitors in beta cell function such as sclerostin [80].

In a preclinical study, we clearly demonstrated that sclerostin production is highly regulated by periostin signaling pathway in osteoblast/osteocyte in response to anabolic stimuli [81, 82]. Moreover, we demonstrated that periostin also directly regulates beta catenin signaling pathway independently of sclerostin. We found that after 5 weeks of intermittent PTH, circulating periostin levels were significantly increased compared to placebo [83]. Recent investigations highlighted periostin as a new molecule talented at pancreatic beta cell regeneration. Periostin injection for 8 weeks enhances glucose tolerance, increases insulin staining in pancreatic tissue, and increases the number of islets [84]. Hence, circulating levels could affect glucose metabolism. It has, however, to be remembered that periostin is not specific to bone and that serum levels represent an additional contribution, and the contribution of each one remains to be determined.

Lastly, because type I collagen is widely distributed in a variety of organs, particularly during pathophysiological conditions such as inflammation and fibrosis, bone matrix protein initially localized in the skeleton can be expressed significantly in soft tissue (Fig. 3). Hence, osteocalcin, periostin, and all others bone matrix proteins can regulate key organs involved in glucose homeostasis (liver, pancreas, adipocyte, smooth, and skeletal muscle) in an endocrine but also in paracrine way.

Conclusion

Developing evidence from preclinical to clinical studies argues for a control of glucose homeostasis through the bone tissue by targeting key organs of the energy metabolism such as pancreas, adipose tissue, liver, and muscle. Bone endocrine function on glucose metabolism cannot be summarized only by osteocalcin secretion and other osteokines—incl. BMPs need to be further investigated. Moreover, osteoclasts, osteoblasts, and osteocytes have a high glucose demand; therefore, the bone tissue should be taken into account in the control loop of glycemia. With a key corollary question: what is the contribution of the bone tissue in the development of insulin resistance and diabetes?

From an evolutionary perspective, organs adaptation has always been driven by one goal: efficient energy conservation and storage that enables survival through periods of food shortage. Accordingly, a tempting hypothesis would be that high bone remodeling and its subsequent bone loss with aging could be a mechanism developed throughout evolution in order to spare energy (and thereby improve longevity). However, these adaptations in the context of our current affluent lifestyles full of food are inappropriate and lead to an excess of energy which leads to many disorders rallied under the so-called metabolic syndrome. Whether maintenance of a normal bone mass could therefore increase glucose consumption and insulin sensitivity to prevent diabetes remains to be investigated.

To conclude, connections or 'networks' between organs including the bone tissue should further be explored to understand the pathophysiology of glucose metabolism and diabetes.

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Compliance with Ethical Standards

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Conflict of interest Nicolas Bonnet declare that he has no conflict of interest.

Ethical approval All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. All procedures performed in studies involving animals were in accordance with the ethical standards of the institution or practice at which the studies were conducted.

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