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REVIEW

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Interrelationships among metabolic syndrome, bone-derived cytokines, and the most common metabolic syndrome-related diseases negatively affecting bone quality

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Abstract

Metabolic syndrome (MetS), as a set of medical conditions including hyperglycemia, hypertension, abdominal obesity, and dyslipidemia, represents a highly prevalent disease cluster worldwide. The individual components of MetS together increase the risk of MetS-related disorders. Recent research has demonstrated that bone, as an endocrine organ, releases several systemic cytokines (osteokines), including fibroblast growth factor 23 (FGF23), lipocalin 2 (LCN2), and sclerostin (SCL). This review not only summarizes current knowledge about MetS, osteokines and the most common MetS-related diseases with a detrimental impact on bone quality (type 2 diabetes mellitus: T2DM; cardiovascular diseases: CVDs; osteoporosis: OP), but also provides new interpretations of the relationships between osteokines and individual components of MetS, as well as between osteokines and MetS-related diseases mentioned above. In this context, particular emphasis was given on available clinical studies. According to the latest knowledge, FGF23 may become a useful biomarker for obesity, T2DM, and CVDs, as FGF23 levels were increased in patients suffering from these diseases. LCN2 could serve as an indicator of obesity, dyslipidemia, T2DM, and CVDs. The levels of LCN2 positively correlated with obesity indicators, triglycerides, and negatively correlated with high-density lipoprotein (HDL) cholesterol. Furthermore, subjects with T2DM and CVDs had higher LCN2 levels. SCL may act as a potential biomarker predicting the incidence of MetS including all its components, T2DM, CVDs, and OP. Elevated SCL levels were noted in individuals with T2DM, CVDs and reduced in patients with OP. The aforementioned bone-derived cytokines have the potential to serve as promising predictors and prospective treatment targets for MetS and MetS-related diseases negatively affecting bone quality.

Keywords Metabolic syndrome, Fibroblast growth factor 23, Lipocalin 2, Sclerostin, Bone health, Type 2 diabetes mellitus, Cardiovascular diseases, Osteoporosis

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Introduction

Metabolic syndrome (MetS) represents a clinical condition characterized by a combination of hyperglycemia, hypertension, abdominal obesity, and dyslipidemia [1]. It is considered a low-grade chronic inflammatory state caused by a complex interaction of genetic and environmental factors [2]. Heritability estimates for MetS range from approximately 10–30% [3]. Environmental factors such as unhealthy diet, physical inactivity, smoking, and stress are closely related to the incidence of MetS [4].

The complex nature of MetS has led to several definitions, including those from the World Health Organization (WHO), American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI), International Diabetes Federation (IDF), with a consensus reached between the AHA/NHLBI and the IDF in 2009 [1]. According to the aforementioned statement, MetS is diagnosed based on the presence of at least three out of five components mentioned below:

1. Abdominal obesity (waist circumference ≥ 102 cm for European men or ≥ 88 cm for European women; ≥ 90 cm for Asian men or ≥ 80 cm for Asian women; alternatively, visceral fat area ≥ 80 cm^2);
2. High serum triglycerides (≥ 150 mg/dL);
3. Low serum high-density lipoprotein (HDL) cholesterol (< 40 mg/dL in men or < 50 mg/dL in women);
4. Hypertension (systolic blood pressure ≥ 130 mmHg and diastolic blood pressure ≥ 85 mmHg);
5. Hyperglycemia (fasting blood glucose ≥ 100 mg/dL).

According to a current meta-analysis by Noubiap et al. [5], the incidence of MetS ranged from 12.5 to 31.4% in global general population of adults. The prevalence of MetS was the highest in Eastern Mediterranean region (36.6%), followed by USA (33.4%) and lowest in Africa region (23.1%). Considering the individual components of MetS, the global prevalence was 45.1% for central obesity, 42.6% for arterial hypertension, 40.2% for low HDL-cholesterol, 28.9% for high triglycerides (TGs), and 24.5% for hyperglycemia. Notably, the incidence rate of MetS increases with age, resulting in a prevalence of 40–45% in people over 50 years of age [6]. These data point to the fact that MetS and its individual components are very widespread worldwide. Furthermore, MetS is often associated with other serious (MetS-related) diseases that can have an unfavorable impact on bone health. Recent studies have shown that bone, as an endocrine organ, is able to secrete several systemic cytokines (osteokines) that may also act as biomarkers predicting the incidence of several disorders. The main aim of this review was not only to summarize current knowledge about MetS, bone-derived cytokines and the most common MetS-related diseases with a negative effect on bone quality (type 2 diabetes mellitus: T2DM; cardiovascular diseases: CVDs; osteoporosis: OP), but also to provide new interpretations of the relationships between osteokines and individual components of MetS, as well as between osteokines and MetS-related disorders, which are currently not available in such a form. In this context, particular emphasis was placed on available clinical studies. Such a review is much more comprehensive and provides up-to-date knowledge in this field.

The most common metabolic syndrome-related diseases affecting bone quality

Individual components of MetS together raise the risk of several serious disorders [7]. The most common MetS-related diseases associated with impaired bone quality and health include T2DM, CVDs, and OP, that will be further considered.

Generally, MetS is linked to T2DM, with hazard ratios ranging from 3.21 to 7.35 depending on the combination of the three different components of MetS [8]. Although T2DM is a multifactorial endocrine disease manifested by chronic hyperglycemia, the majority of affected individuals have insulin resistance, relative insulin deficiency and MetS before the onset of T2DM [9]. In response to hyperglycemia, insulin exerts its anabolic effects by inhibiting lipolysis and hepatic gluconeogenesis, whereas increasing glucose uptake in the liver, muscle, and adipose tissue. When insulin resistance develops in adipose tissue, insulin-mediated inhibition of lipolysis is impaired. The resulting high concentrations of free fatty acids elevate the synthesis of cholesterol esters and TGs and subsequently the production of very low density lipoproteins rich in TGs [10]. These alterations in lipoprotein concentrations may represent a hallmark of atherogenic dyslipidemia caused by insulin resistance in MetS [11]. Many of the most serious complications of T2DM are due to oxidative stress and can be classified as macrovascular and microvascular. Macrovascular complications include myocardial infarction, stroke, peripheral vascular disease, and diabetic foot. Microvascular complications mainly involve diabetic neuropathy, nephropathy, retinopathy, and diabetic bone disease. Diabetic bone disease is considered to be secondary OP caused by T2DM. Affected individuals have altered bone mineral density (BMD), worse bone quality, elevated risk of fragility fractures at specific sites, and prolonged fracture healing [12–14].

MetS can be a significant factor consistent with CVDs, a group of disorders of the heart and blood vessels that involve especially coronary heart disease, peripheral artery disease, cerebrovascular disease, aortic atherosclerosis [15]. Many studies and meta-analyses noted a higher risk of developing CVD-related events in individuals with

MetS [16–18]. Guembe et al. [19] found that the risk of these events varied with combinations of individual MetS components and elevated with a higher number of components. Several studies have demonstrated an association between CVDs and OP. According to Park et al. [20], reduced BMD was associated with a greater risk of atherosclerotic CVD-related death, myocardial infarction, and ischemic stroke. A meta-analysis by Ge et al. [21] showed that heart failure was consistent with an increased risk of all fractures, especially hip fractures.

The relationship between MetS and OP has been known for a long time and is heterogeneous [22]. Generally, OP is characterized by decreased BMD, disrupted bone microarchitecture, and higher risk of fragility fractures. Primary OP type 1 is associated with menopause, while primary OP type 2 occurs after the age of 75 and is diagnosed in a ratio of 1:2 in men and women [23, 24]. During menopause, osteoprotective effect of estrogen is weakened that leads to raising expression of pro-inflammatory cytokines, promoting osteoclastogenesis. In addition, estrogen deficiency not only directly influences the differentiation of precursor cells less toward osteoblasts and more toward active osteoclasts, but may also affect their cellular energy. Increased adiposity and inflammation after menopause may also be related to bone loss [25–27]. A gender-specific trend between MetS, BMD and osteoporotic fractures was noted, possibly due to factors consistent with body composition and hormonal status of individuals [28–30]. According to Yu et al. [31], women with MetS had higher rates of fracture risk compared to those without MetS. On the contrary, men with MetS had a negative association with bone fractures. Liu et al. [32] found that the MetS was associated with higher risk of OP in women but not in men. In this context, it is important to mention that women and men have different bone metabolism in old age. In men with OP, the rate of bone formation relative to bone resorption did not increase compared to the rate in women with OP [33].

Associations between individual components of metabolic syndrome and bone health

In general, MetS can adversely affect multiple organs, including bones. Each component of MetS clearly influences bone mass as well as bone metabolism. Several mechanisms of action can be proposed for the effects of individual components of MetS on bone health (Fig. 1).

Abdominal obesity is a significant contributing factor to negative association with BMD, suggesting that fat (especially visceral fat) is detrimental to bone mass [34]. Moreover, visceral fat is also considered an endocrine organ that releases adipokines and cytokines, including pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β), interleukin 6 (IL-6). They can stimulate osteoclast differentiation and bone resorption through activation of receptor activator of NF-κB ligand (RANKL)/receptor activator of NF-κB (RANK)/osteoprotegerin (OPG) pathway [35, 36]. Obesity is also associated with bone marrow adipogenesis which depletes mesenchymal stem cells available to generate osteoblasts [37]. Visceral fat accumulation, alterations in lipid profile and blood pressure are correlated with low levels of serum osteocalcin (a sensitive marker of bone formation) in adult population [38]. In addition, obesity induces the generation of oxidative stress which increases osteoclastogenesis and reduces osteoblastogenesis, resulting in altered bone microarchitecture and bone loss [39, 40]. Taking into account other factors with a negative impact on bone metabolism, elevated leptin concentrations accelerating bone resorption and decreasing bone formation were recorded, leading to raised risk of fractures [41]. Moreover, higher leptin production and/or lower adiponectin secretion may contribute to macrophage accumulation in adipose tissue [42]. Macrophages (another source of pro-inflammatory factors) further contribute to deleterious effects of pro-inflammatory cytokines on bone metabolism [37]. Thus, low-grade chronic inflammation is a hallmark of obesity [43]. In general, obesity is linked to normal or increased BMD; however, it is associated with elevated risk of fragility fractures at specific sites, which is termed "obesity paradox". In fact, obese individuals are at increased risk of fractures of the humerus, ankle, upper leg, elbow, vertebrae, and rib. On the contrary, obesity is a protective factor against hip, pelvic, and wrist fractures in elderly patients. Therefore, the relationship between obesity and fracture risk is more complex than previously thought. Implementation of better diagnostic tools to predict body fat percentage and assess comprehensive bone health including fragility fracture risk in obese subjects (e.g. waist circumference: WC, waist to hip ratio: WHR, high-resolution peripheral quantitative computed tomography: HR-pQCT, trabecular bone score: TBS; lumbar spine BMD/BMI ratio) can be considered an important clinical and future priority that could improve fracture prevention in this group of patients [44–49].

Dyslipidemia manifests itself by low HDL cholesterol and high TG levels. Disorders of lipid metabolism are consistent with increased levels of oxidized lipids. Lipid oxidation (as an index of oxidative stress correlated with low HDL levels) stimulates adipocyte differentiation while suppressing osteoblast differentiation through upregulation of peroxisome proliferator-activated receptor γ (PPARγ). PPARγ is a member of the nuclear hormone receptor subfamily of transcription factors expressed in adipocytes to improve and mediate adipocyte differentiation [50]. Activated PPARγ

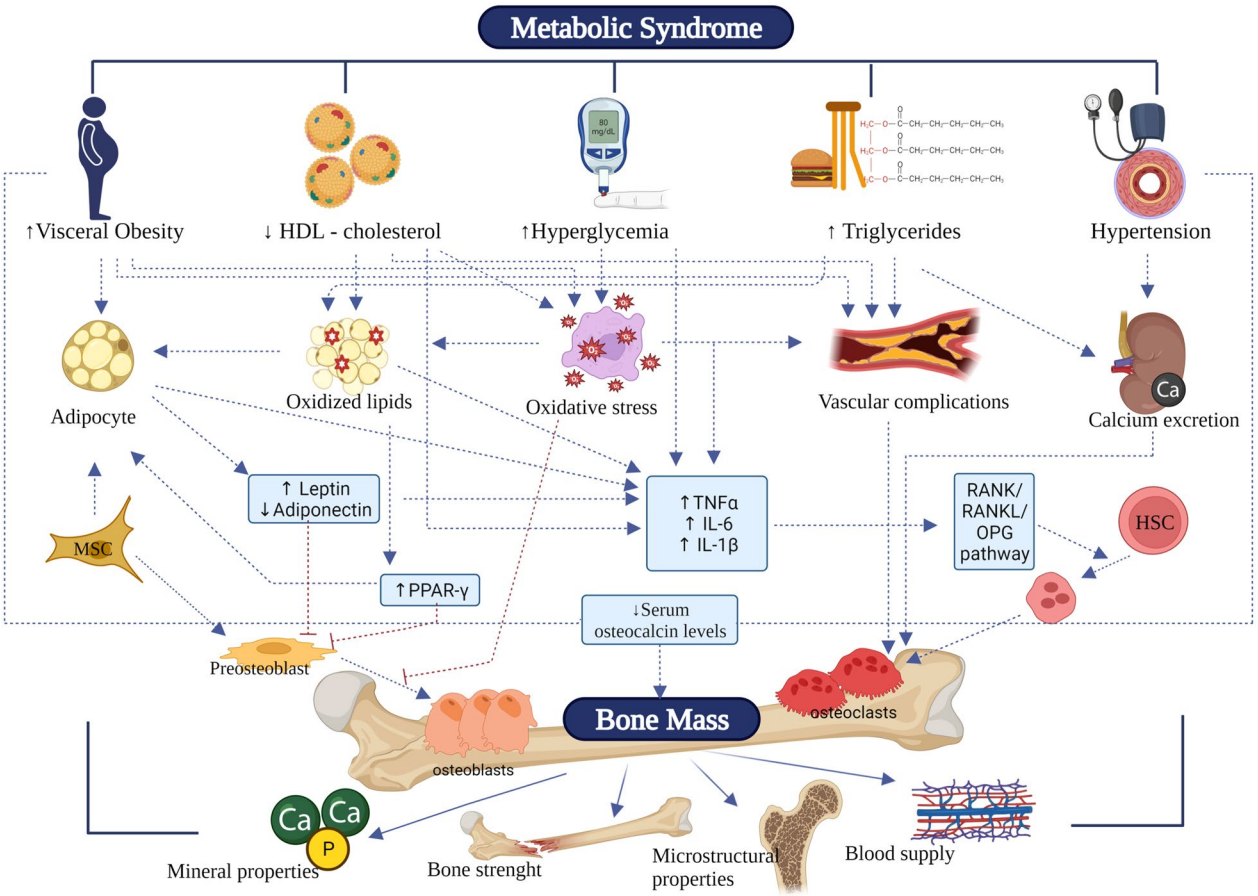

Fig. 1 Individual components of MetS including visceral obesity, low serum high-density lipoprotein (HDL) cholesterol, hyperglycemia, high serum triglycerides (TGs), and hypertension affect bone health through different mechanisms. Visceral fat releases adipokines and pro-inflammatory cytokines, including tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), interleukin 1β (IL-1β), which stimulate osteoclast differentiation through activation of receptor activator of NF-κB ligand (RANKL)/receptor activator of NF-κB (RANK)/osteoprotegerin (OPG) pathway. Obesity also depletes mesenchymal stem cells (MSC) for adipocyte formation at the expense of osteoblasts. Obese individuals exert elevated leptin and decreased adiponectin levels, and higher oxidative stress, which ultimately suppress osteoblastogenesis and stimulate osteoclastogenesis. Low HDL is correlated with increased levels of oxidative stress and oxidized lipids that stimulate adipocyte differentiation while suppressing osteoblast differentiation through upregulation of peroxisome proliferator-activated receptor γ (PPARγ). In addition, low HDL stimulates osteogenic activity in vascular cells. Elevated TGs, usually present with low HDL cholesterol, can induce endothelial cell dysfunction and potentiate atherogenic changes. Hyperglycemia causes enhanced inflammatory response, accumulation of advanced glycation end products (AGEs), and disturbances in calcium (Ca) metabolism, favoring bone resorption over bone formation. Arterial hypertension affects bone mainly through increased excretion of Ca in the urine, resulting in activation of parathyroid hormone (PTH), thereby raising bone resorption. Finally, multiple mechanisms involving visceral fat accumulation, alterations in lipid profile and blood pressure are correlated with lower serum osteocalcin levels, suggesting reduced bone formation (Created with BioRender.com)

has been reported to enhance adipocyte differentiation and inhibit osteoblast formation in various mesenchymal cell lines and bone marrow [51]. In general, HDL inhibits osteogenic activity in vascular cells by inducing pro-inflammatory cytokines. Oxidation of HDL makes it pro-osteogenic, suggesting that HDL regulates osteoblast differentiation [52]. On the contrary, oxidized low-density lipoprotein (LDL) cholesterol particles and excess free fatty acids in dyslipidemia can uncouple bone remodeling, favoring bone resorption [53]. Overall, elevated TG levels can be negatively correlated with femoral neck BMD in postmenopausal women [54]. In addition, high TGs were also negatively correlated with BMD at all sites in adolescent girls [55].

Arterial hypertension is known to be an important factor affecting bone loss. As a result of hypertension, there is an increased excretion of calcium (Ca) in the urine due to competition between sodium (Na) and Ca ions in the renal proximal tubule [56]. Urinary excretion of Ca reduces the level of circulating Ca, resulting in activation of parathyroid hormone (PTH), thereby increasing bone resorption [57, 58]. Therefore, it can be hypothesized that

maintenance of Ca levels provides protective effects on bone strength and reduces the incidence of bone fractures in hypertension by limiting urinary Ca loss [59]. Sympathetic tone, vascular perturbations, cytokines, renin/angiotensin/aldosterone system, and vitamin D were described as further aspects connecting OP, hypertension, and related CVDs [60]. According to Li et al. [61], the risk of fragility fractures was higher in subjects with hypertension compared to healthy individuals. A cross-sectional study by Li et al. [62] revealed a positive association between hypertension and lumbar spine BMD in both postmenopausal women and older men. In general, thiazide diuretics (thiazides) are well-tolerated and effective antihypertensive drugs that are considered candidates for the prevention of postmenopausal bone loss due to their ability to reduce urinary Ca excretion [63]. Furthermore, they are known to have a positive effect on BMD [64–66] and their use is associated with a reduced risk of OP-related fractures [67–69]. A meta-analysis of Cheng et al. [70] showed that patients treated with thiazides had significantly higher serum Ca levels, lower urinary Ca levels, and unchanged BMD. The recent findings by van der Burgh et al. [71] suggest their positive impacts on lumbar spine BMD but not on lumbar spine TBS. Therefore, reduced fracture risk after thiazide therapy can be explained by elevated bone mass rather than improved bone microarchitecture. Other antihypertensives such as angiotensin receptor blockers (ARBs) and selective β-adrenergic receptor blockers might also improve BMD. A recent meta-analysis by Langerhuizen et al. [72] revealed that, in addition to thiazide diuretics, ARBs and β-blockers can reduce the risk of hip fracture. Additionally, nonselective β-adrenergic receptor blockers and dihydropyridine Ca channel blockers were found to have no significant relationship with BMD or bone strength. Since negative results have been reported on the impact of loop diuretics and α-adrenergic receptor blockers on OP indicators, they are not recommended for patients who are at increased risk of OP or already have OP [57, 73–75].

Hyperglycemia can cause bone loss through increased inflammatory response and disturbances in Ca metabolism. Impaired insulin secretion and/or insulin action due to T2DM elevates levels of TNF-α and IL-6 [59]. Accumulation of advanced glycation end products (AGEs) induces apoptosis of mesenchymal stem cells and leads to higher bone resorption, resulting in poorer bone quality and strength [76]. The impact of hyperglycemia on bone metabolism is also dependent on insulin and insulin-like growth factor 1 (IGF-1) deficiency. As a humoral factor, IGF-1 acts as a vital anabolic signal to increase bone formation. Therefore, IGF-1 deficiency is associated with low bone size, decreased BMD, growth retardation, and development of OP [77]. Glycosuria is an indirect consequence of hyperglycemia. According to Schneider et al. [78], glycosuria caused defective reabsorption of both Ca and glucose in the renal proximal tubule, leading to hypercalciuria. Correspondingly, circulating Ca levels were reduced, which was reflected by impaired bone quality and bone loss [79]. It is widely recognized that sodium-glucose cotransporter 2 (SGLT2) inhibitors can also induce glycosuria [80]. However, due to its unique mechanism of glucose regulation through renal proximal tubules, SGLT2 inhibitors may also affect Ca and phosphate (P) homeostasis, potentially leading to reduced BMD. Furthermore, they demonstrated an indirect increase in bone turnover through weight loss [81]. Current data suggest that the effect of SGLT2 inhibitors on bone turnover and BMD varies between drugs. Canagliflozin and ertugliflozin might elevate bone resorption [82], while dapagliflozin and empagliflozin might not have any effect on bone turnover [83–85]. Bilezikian et al. [86] revealed significant reduction in total hip BMD and an increase in markers of bone formation and bone resorption in T2DM subjects treated with canagliflozin. Conversely, dapagliflozin had no effect on BMD or bone formation and bone resorption markers in individuals with T2DM [83]. The impact of SGLT2 inhibitors on fracture risk remains controversial [81, 87, 88].

Bone cells are known to be able to secrete various bioactive substances that can regulate bone remodeling. In addition, they can be released into systemic circulation and affect distant organs such as the pancreas, testes, brain, kidneys and regulate global energy homeostasis [89, 90]. In this review, bone-derived cytokines, namely fibroblast growth factor 23 (FGF23), lipocalin 2 (LCN2), and sclerostin (SCL) are further considered because they are intimately involved in bone metabolism, metabolic functions, and may also act as biomarkers predicting the prevalence of multiple disorders, as well as the progression of their complications. The present findings indicate clinical relevance of aforementioned cytokines as prognostic tumor biomarkers and potential therapeutic targets in bone metastases [91]. This review further focuses on aspects linking FGF23, LCN2, SCL to individual components of MetS, as well as to the most frequently occurring MetS-related disorders (T2DM, CVDs, OP) that affect bone quality. Such relationships appear only sporadically in the scientific literature.

Links among fibroblast growth factor 23, metabolic syndrome, and the most common metabolic syndrome-related diseases affecting bone quality

Fibroblast growth factor 23 (FGF23) is a bone-derived protein belonging to a subfamily of endocrine FGFs [92]. The *FGF23* gene is located on human chromosome 12p13, containing 3 coding exons [93]. Product

of this gene is a 32-kDa glycoprotein, which consists of 251 amino acid residues including a signal sequence (24 amino acids), an N-terminal hydrophobic region (155 amino acids), and a specific carboxy-terminal sequence (72 amino acids; Fig. 2) [94]. FGF23 is predominantly secreted by osteocytes and osteoblasts, and is able to target cells in distant organs (e.g. kidneys, heart) [92, 95]. Binding of FGF23 to target cells needs a receptor complex containing of FGF tyrosine kinase receptors (FGFRs subtypes 1c,3c, or 4c) and the transmembrane protein α-Klotho, a co-receptor for FGF23 [96]. The secretion of FGF23 is stimulated by a plethora of humoral factors, such as vitamin D, Ca, P, PTH, and pro-inflammatory cytokines [94]. FGF23 plays a key role as an auto-/paracrine regulator of energy metabolism and mineral homeostasis [97]. According to Martin et al. [98], FGF23 acts as a counterregulatory phosphaturic hormone to maintain P homeostasis in response to 1,25-dihydroxyvitamin D (1,25(OH)2D), which can promote *FGF23* expression [99]. FGF23 can inhibit the expression of renal 1α- hydroxylase (CYP27B1), that converts 25-hydroxyvitamin D into 1,25-dihydroxyvitamin D3 (the active form), subsequently interfering with Ca homeostasis [100].

Mirza et al. [101] pointed out the relationships between FGF23 and MetS incidence as well as between FGF23 and individual components of MetS. According to Hu et al. [102], FGF23 levels were significantly higher in overweight/obese individuals. Moreover, FGF23 levels were positively associated with body mass index (BMI), WC, and visceral fat area (VFA) in both postmenopausal women and men. Positive correlations between VFA and FGF23, WC, and FGF23 were also identified by Xu et al. [103] and Mirza et al. [101]. Hanks et al. [104] found a positive association of FGF23 with BMI and WC in

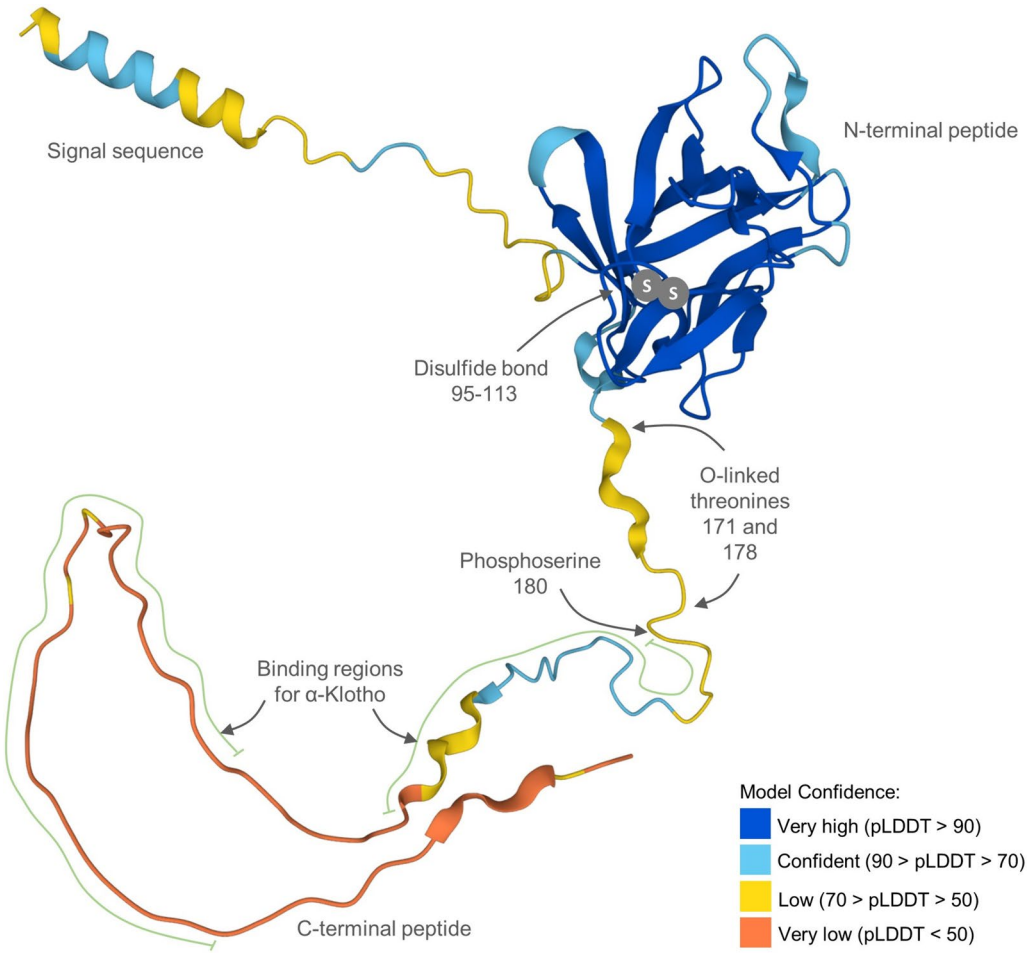

Fig. 2 Human FGF23 structure prediction according to AlphaFold Protein Structure Database (RRID: SCR_023662; [264, 265]). 3D visualization of FGF23 structure prediction with colored per-residue confidence metric (pLDDT) is shown. The structures of the signal sequence and N-terminal peptide demonstrate the highest confidence score. Positions of glycosylation, phosphorylation, and disulfide bond on FGF23 molecule are illustrated according to the database UniProt (RRID: SCR_002380). Binding regions for α-Klotho are labeled according to Suzuki et al. [266]

subjects with normal renal function. A study of Streicher et al. [105] suggests that a vitamin D receptor-dependent mechanism underlies FGF23 regulation of fat accumulation and distribution. In addition, a feedback effect of adipose tissue on FGF23 levels may also be present, as animal studies have shown stimulatory effects of adipokines (such as leptin) on FGF23 expression in bone [106].

Higher TGs were also consistent with increased FGF23 levels independently of age, BMI, hypertension, or diabetic state [101, 107]. On the other hand, several studies did not find any correlation between FGF23 and TGs [108, 109]. According to a cross-sectional study of Montford et al. [110], higher FGF23 levels were related to dyslipidemia (including lower HDL cholesterol) in patients with chronic hemodialysis. Similarly, raised FGF23 levels were associated with 7–22% lower HDL cholesterol [101]. However, cohort studies by Ebert et al. [108] and Yamamoto et al. [109] demonstrated no correlation between FGF23 and HDL cholesterol.

Elevated levels of FGF23 may also be linked to hypertension. According to Andrukhova et al. [111], FGF23 can serve as a key regulator of renal Na reabsorption and plasma volume, and this fact can contribute to the association between FGF23 and cardiovascular risk in patients with chronic kidney disease (CKD). FGF23 may also participate in the pathogenesis of hypertension through an activation of the renin-angiotensin-aldosterone system [112]. Additionally, Drew et al. [113] have shown that increased FGF23 levels were related to prevalent and incident hypertension, as well as higher systolic blood pressure in older adults. On the other hand, Ebert et al. [108] did not find a correlation between FGF23 and blood pressure. Table 1 shows the relationships between bone-derived cytokines, including FGF23, and individual components of MetS.

Most clinical researches revealed elevated levels of circulating FGF23 in patients with T2DM and CKD [114, 115]. However, a study by Tunon et al. [116] did not confirm this association. Levels of FGF23 were found to be higher also in prediabetic state and in normal blood glucose patients with a family history of first-degree diabetes [117, 118]. Moreover, T2DM was closely associated with an increase in FGF23 from midlife to late life [119]. According to Hanks et al. [104] and Garland et al. [120], FGF23 was positively related to insulin resistance. Conversely, Wojcik et al. [121] and Holecki et al. [122] reported an inverse correlation or no association. A study of Bar et al. [123] suggests that insulin suppresses the production of FGF23 and patients with hyperinsulinemia should have low levels of FGF23. However, a chronic inflammatory state, often present in T2DM patients, may overrule suppressive effect of hyperinsulinemia, resulting in higher FGF23 levels [124]. There are no data supporting a direct role of FGF23 in glucose and lipid metabolism [125], although FGF23 may act indirectly by regulating the stability of P levels [126]. However, increased FGF23 was strongly associated with a higher risk of cardiovascular morbidity and mortality in T2DM patients, and a close relationship was found between FGF23 and diabetic complications [115, 125, 127].

CVD is the leading cause of death in patients with CKD [128]. As elevated FGF23 levels are commonly found in CKD patients, FGF23 has also gained a significant interest due to its strong association with CVDs. Increased FGF23 concentrations were associated with prevalent CVDs in older women stratified by CKD, but also in all subjects and non-CKD patients [129]. Higher FGF23 levels were related to total body atherosclerosis as well as vascular dysfunction [101, 130]. In patients with coronary artery disease and heart failure with reduced ejection fraction, FGF23 was consistent with CVD-related events [131, 132]. In addition, patients stabilized after acute coronary syndrome with elevated FGF23 had an increased risk of death, hospitalization due to heart failure, myocardial infarction, or stroke [133]. Raising levels of FGF23 were also related to the severity of coronary artery calcification; however, they were not associated with carotid artery atherosclerosis in hemodialysis patients [134, 135]. Considering stroke, higher FGF23 was found to be an independent risk factor for cardioembolic stroke but not other stroke subtypes in adults [136]. Several studies suggest an association between higher FGF23 level and left ventricular hypertrophy (LVH) or left ventricular mass (LVM) in patients with CKD and hemodialysis, but also in general population [137–139]. It is known that LVH predicts CVD-related events. However, CKD patients had excessive cardiomyocyte production of FGF23 leading to upregulation of FGFR4 and activation of the calcineurin-NFAT pathway [140]. A recent study by Watanabe et al. [141] showed that not serum but cardiac FGF23 levels were altered also in early stage of LVH without CKD, and the renin-angiotensin-aldosterone system may also play an important role. Moreover, several studies suggest that high FGF23 may follow, rather than induce, myocardial disease under certain conditions, and some beneficial cardiovascular effects of FGF23 in primary cardiomyocytes have been described. Therefore, further research on FGF23 in relation to CVDs is needed [142].

Studies examining the association between FGF23 and BMD reported inconsistent findings. In CKD patients on dialysis, FGF23 was negatively correlated with lumbar spine BMD [143–145] and/or both lumbar spine and femoral neck BMD [146, 147]. On the other hand, Torres et al. [148], Desjardins et al. [149], Zheng et al. [150] did

Table 1 Relationships between bone-derived cytokines and individual components of MetS

Cytokine	MetS component	Subjects (*N*)	Relationships between the cytokine and the MetS component	*P* value	Ref.
FGF23	Obesity	Normoglycemic men (597) with normal renal function	0.71% increase in FGF23 levels at 10% increase in VFA	0.001	[102]
		Postmenopausal normoglycemic women (591) with normal renal function	0.94% increase in FGF23 levels at 10% increase in VFA	0.001	[102]
		Adult men and women (1040)	FGF 23 positively associated with WC (β = 3.02)	0.004	[104]
		Elderly men and women (946)	2% increase in WC at 10% increase in FGF23 level	< 0.01	[101]
		Middle aged men and women (1179)	FGF23 positively correlated with VFA (β = 0.089); increase in FGF23 level (1 SD) associated with VFA (OR 1.326)	0.035, < 0.001	[103]
	Triglycerides	Middle aged men (1261)	Differences in FGF23 levels from 1.6 to 7.2 RU/mL depending on triglycerides quartile	< 0.01	[107]
		Elderly men (964)	3% increase in triglycerides at 10% increase in FGF23 level	< 0.001	[101]
		Middle aged men and women (1046)	No correlation between FGF23 and triglycerides	0.962	[108]
		Elderly men and women (73)	No correlation between FGF23 and triglycerides	0.29	[109]
	HDL cholesterol	Elderly men and women (73)	No correlation between FGF23 and HDL	0.35	[109]
		Middle aged men and women (1046)	No correlation between FGF23 and HDL	0.054	[108]
		Hemodialysis patients (654)	Higher FGF23 levels associated with lower HDL (β = − 2.14)	0.03	[110]
	Hypertension	Middle aged men and women (1046)	No correlation between FGF23 and blood pressure	0.943	[108]
		Older men and women (2496)	2-fold higher FGF23 associated with prevalent baseline hypertension (OR 1.46) and incident hypertension (HR 1.18)	< 0.05	[113]
		Middle aged men (1261)	Difference in FGF23 levels of 6.0 RU/ml in the presence of hypertension	< 0.01	[107]
		Elderly men and women (73)	No association between FGF23 and hypertension	0.087	[109]
LCN2	Obesity	Older women (705)	Women in the highest LCN2 quartile had higher BMI (28.9 ± 4.8) compared to women in the lowest quartile (25.8 ± 4.0)	< 0.05	[177]
		Adult women and men (100 lean, 80 overweight, 49 obese)	LCN2 was positively correlated with BMI (r = 0.394) and WC (r = 0.404)	< 0.001	[180]
		Postmenopausal women with prediabetes (88)	Strong positive correlation between LCN2 and BMI (r = 0.30) and WC (r = 0.29)	0.004, 0.006	[181]
		Men (169) and postmenopausal women (92) who underwent coronary angiography	LCN2 was positively correlated with BMI (r = 0.195) and WC (r = 0.164)	0.011, 0.033	[178]
		Healthy women and men (53)	LCN2 was positively correlated with BMI (r = 0.402)	0.02	[179]
		Obese women (188)	LCN2 was positively correlated with BMI (r = 0.205) but not with WC	0.005, 0.49	[182]
		Normal (101) and overweight/obese (136) T2DM patients	LCN2 was positively correlated with BMI (r = 0.546)	< 0.001	[183]
		Patients with coronary heart disease (49) and controls (42)	No correlation between LCN2 and WC (r = 0.18)	0.161	[185]
		Healthy men (100)	No correlations between LCN2 and BMI and WC	0.88, 0.98	[184]
	Triglycerides	Older women (705)	Women in the highest LCN2 quartile had higher triglycerides (148.6 ± 57.1 mg/dL) compared to women in the lowest quartile (120.6 ± 52.2 mg/dL)	< 0.05	[177]
		Men (169) and postmenopausal women (92) who underwent coronary angiography	LCN2 was positively correlated with triglycerides (r = 0.215)	0.005	[178]

Table 1 (continued)

Cytokine	MetS component	Subjects (*N*)	Relationships between the cytokine and the MetS component	*P* value	Ref.
		Healthy women and men (53)	LCN2 was positively correlated with triglycerides ($r = 0.4811$)	0.01	[179]
		Obese women (188)	LCN2 was positively correlated with triglycerides ($r = 0.214$)	0.003	[182]
		Normal (101) and overweight/obese (136) T2DM patients	LCN2 was positively correlated with triglycerides ($r = 0.325$)	< 0.001	[183]
		Patients with coronary heart disease (49) and controls (42)	No correlation between LCN2 and triglycerides	0.578	[185]
		Healthy men (100)	No correlation between LCN2 and triglycerides	0.21	[184]
	HDL cholesterol	Older women (705)	Women in the highest LCN2 quartile had lower HDL cholesterol (54.2 ± 14.7 mg/dL) compared to women in the lowest quartile (60.4 ± 15.7 mg/dL)	< 0.05	[177]
		Adult women and men (100 lean, 80 overweight, 49 obese)	LCN2 was negatively correlated with HDL cholesterol ($r = -0.2$)	0.002	[180]
		Healthy women and men (53)	LCN2 was negatively correlated with HDL cholesterol ($r = -0.4034$)	0.03	[179]
		Obese women (188)	LCN2 was negatively correlated with HDL cholesterol ($r = -0.299$)	< 0.001	[182]
		Normal (101) and overweight/obese (136) T2DM patients	LCN2 was negatively correlated with HDL cholesterol ($r = -0.237$)	< 0.001	[183]
		Patients with coronary heart disease (49) and controls (42)	LCN2 was negatively correlated with HDL cholesterol ($r = -0.3$)	0.016	[185]
		Healthy men (100)	LCN2 was negatively correlated with HDL cholesterol ($r = -0.29$)	0.004	[184]
	Hypertension	Older women (705)	No differences in blood pressure between LCN2 quartiles	NS	[177]
		Adult women and men (100 lean, 80 overweight, 49 obese)	LCN2 was positively correlated with systolic ($r = 0.154$) but not with diastolic blood pressure	0.017, 0.637	[180]
		Obese women (188)	LCN2 was positively correlated with systolic ($r = 0.325$) but not with diastolic blood pressure	< 0.001, 0.13	[182]
		Normal (101) and overweight/obese (136) T2DM patients	LCN2 was positively correlated with systolic ($r = 0.189$) and diastolic ($r = 0.201$) blood pressure	0.003, 0.002	[183]
		Patients with coronary heart disease (49) and controls (42)	No correlations between LCN2 and systolic and diastolic blood pressures	0.057, 0.214	[185]
		Patients with essential hypertension (62) and controls (16)	LCN2 levels were higher in patients with essential hypertension than in controls (85.0 ± 37.6 ng/mL vs. 43.8 ± 13.1 ng/mL)	< 0.001	[187]
		Healthy men (100)	No correlations between LCN2 and systolic and diastolic blood pressures	0.68, 0.92	[184]
SCL	Obesity	Older men (694)	Higher SCL was associated with severity of MetS (OR 1.24 per SD increase)	< 0.05	[220]
		Older men (115) and postmenopausal women (134)	SCL was positively associated with vertebral bone marrow fat in older men (52.2% in the lowest tertile of serum SCL, 56.3% in the highest tertile) but not women	< 0.01, NS	[221]
		Postmenopausal women (352)	SCL was positively correlated with abdominal fat ($r = 0.18$)	0.018	[222]
		Children and adolescents (1325)	SCL level in children with obesity increased with BMI standard deviation score ($r = 0.035$)	< 0.001	[223]
		Adolescent females with increased physical activity (73)	SCL was positively correlated with body fat ($r = 0.38$)	< 0.05	[226]
		Morbidly obese patients (94)	SCL was positively associated with WC ($\beta = 0.028$) and positively correlated with WC ($r = 0.238$), waist-to-hip/waist-to-height ratios ($r = 0.315$; $r = 0.234$), VFA and subcutaneous fat area ($r = 0.220$; $r = 0.228$)	0.016, < 0.05	[224]

Table 1 (continued)

Cytokine	MetS component	Subjects (*N*)	Relationships between the cytokine and the MetS component	*P* value	Ref.
		Obese (31), overweight (23) and normal (21) subjects	SCL levels were lower in obese subjects versus controls (1.02 ± 0.45 vs. 1.58 ± 0.83 ng/mL)	0.014	[225]
	Triglycerides	Adult patients (2054)	Positive association between SCL and triglycerides (β = 0.05)	0.038	[231]
		Adult patients (502617)	Positive association between BMD-increasing SOST variants (rs7209826 and rs188810925) and triglycerides (9.58 mg/dL higher)	0.02	[232]
	HDL cholesterol	Adult patients (2054)	SCL was inversely related to HDL cholesterol (β = − 0.08)	< 0.001	[231]
	Hypertension	Adult patients (3015)	Positive association between SCL and hypertension (OR 1.19)	0.03	[231]
		Adult patients (502617)	Positive association between BMD-increasing SOST variants (rs7209826 and rs188810925) and hypertension (OR 1.12)	< 0.001	[232]

BMD bone mineral density, *BMI* body mass index, *FGF23* fibroblast growth factor 23, *HDL* high-density lipoprotein, *HR* hazard ratio, *LCN2* lipocalin 2, *LDL* low-density lipoprotein, *MetS* metabolic syndrome, *OR* odds ratio, *r* correlation coefficient, *SCL* sclerostin, *SD* standard deviation, *T2DM* type 2 diabetes mellitus, *VFA* visceral fat area, *WC* waist circumference

not find any correlation between FGF23 and BMD. For non-CKD individuals, FGF23 showed negative relationships with lumbar spine or proximal femur BMD [151] and/or with femoral neck BMD [152]. However, other studies did not reveal an association between FGF23 and lumbar spine BMD [153] and/or hip BMD [154]. Accordingly, BMD was not correlated with FGF23 in premenopausal women [155]. In men, elevated FGF23 levels were associated with higher total hip and lumbar spine BMD [154] or the correlation between FGF23 and BMD became nonsignificant after adjustment for established confounding variables [156]. Furthermore, higher FGF23 levels were consistent with an increased fracture risk in men [157]. In a study of Isakova et al. [158], no associations were found between FGF23 levels and bone loss or fracture risk. Using a Mendelian randomization analysis, FGF23 was inversely related to femoral neck and heel BMD, but not to lumbar spine BMD and fracture risk [159, 160]. In addition to BMD, a relationship between C-terminal FGF23 and bone microarchitecture has been reported in patients with OP [161]. FGF23 negatively correlated with relative bone volume as well as trabecular number at the distal radius and tibia. No association between FGF23 and BMD (assessed by DXA) was noted in this study. The relationships between bone-derived cytokines, including FGF23, and T2DM, CVDs, OP are presented in Table 2.

Taking into account the information presented in this chapter, we can conclude that FGF23 levels are significantly increased in patients suffering from obesity, T2DM, and CVDs. In obese individuals, FGF23 levels are positively associated with BMI, WC, and VFA. In patients with T2DM, raising FGF23 is strongly related to a higher risk of cardiovascular morbidity and mortality, and a close relationship between FGF23 and diabetic complications has been determined. Elevated FGF23 levels are strongly linked to total body atherosclerosis, vascular dysfunction, acute coronary syndrome, cardioembolic stroke, and LVH. Furthermore, increased circulating FGF23 is commonly found in CKD patients, so it can be used as a predictive factor to evaluate the progression of this disease. On the contrary, studies investigating the association between FGF23 and BMD report inconsistent findings.

Links among lipocalin 2, metabolic syndrome, and the most common metabolic syndrome-related diseases affecting bone quality

Lipocalin 2 (LCN2), a novel adipokine, is also termed as neutrophil gelatinase-associated lipocalin (NGAL) [95]. It belongs to lipocalin superfamily, a large group of transporters of hydrophobic ligands in circulation, including various steroids, hormones, prostaglandins, and retinoids [162]. Human LCN2 protein is encoded by the *LCN2* gene located at the chromosome locus 9q34.11 [163]. Product of this gene, a soluble secretory glycoprotein, circulates as a 25 kDa monomer, a 46 kDa disulphide-linked homodimer and a 135-kDa disulphide-linked heterodimer [164]. The LCN2 structure is comprised of an eight stranded β-barrel that represents the internal ligand-binding site. This site is larger and more polar than in other lipocalin proteins and allows LCN2 to form large molecule complexes. At the N-terminal region of the human LCN2 protein, there is a 20-amino acid signal peptide, which is detached from the molecule before release [162] (Fig. 3). In humans, LCN2 is released by

Table 2 Relationships between bone-derived cytokines and T2DM, CVDs, OP

Cytokine	Disease	Subjects (*N*)	Relationships between the cytokine and the disease	*P* value	Ref.
FGF23	T2DM	Men and women with decreased kidney function and with T2DM (1820), without T2DM (1936)	Higher FGF23 levels in T2DM patients versus non-diabetic patients (172.4 [114.3–277.2] vs. 121.9 [84.0–198.8] RU/mL)	< 0.05	[114]
		Adult men and women with T2DM (288) and without T2DM (288)	Higher FGF23 levels in T2DM patients than in patients without diabetes (75.6 [61.3–91.8] vs. 70.8 [58.0–85.8] RU/mL)	< 0.001	[115]
		Men and women with T2DM (173) and without T2DM (531)	No difference in FGF23 levels in diabetic vs. non-diabetic patients	0.323	[116]
		Men and women with obesity (41), with obesity and prediabetes (39)	Prediabetic individuals had higher FGF23 levels than obese controls (10.4 ± 10.7 vs. 5.8 ± 7.3 pg/mL)	< 0.05	[117]
	CVDs	Older women (659)	FGF23 was related to CVDs in all participants (OR 1.23 per 1 SD increase), CKD patients (OR 1.42), and without CKD (OR 1.10)	< 0.0001, < 0.05	[129]
		Elderly men and women (306)	Higher FGF23 level was associated with an increase of atherosclerosis score (OR 1.43 to 3.01)	< 0.05	[130]
		Patients with coronary artery disease and heart failure (485), controls (455)	FGF23 was linked to cardiovascular events (myocardial infarction/stroke, heart failure, sudden cardiac death), OR 1.265	< 0.001 (FDR)	[131]
		Patients with stable ischemic heart disease (3627)	FGF23 was associated with an increased risk of cardiovascular death or heart failure (quartile 4 HR 1.73)	0.02	[132]
		Patients stabilized after an acute coronary syndrome (4947)	Elevated FGF23 concentration was associated with cardiovascular death or heart failure hospitalization (HR 2.35), all-cause mortality (HR 2.27), myocardial infarction or stroke (HR 1.42)	< 0.001	[133]
		Hemodialysis patients (229)	FGF23 was positively correlated with coronary artery calcification ($r = 0.218$)	0.001	[134]
		Hemodialysis patients (74)	FGF23 was positively correlated with the progression of coronary artery calcification ($r = 0.51$) in the low baseline group (CACS ≤ 30)	0.006	[135]
		Adult men and women with incident stroke (615) and controls (936)	A graded association of FGF23 with risk of cardioembolic stroke (quartile 4 HR 2.52)	0.04	[136]
		Older men and women (2255)	Higher FGF23 was associated with greater left ventricular mass in all participants (β = 6.71 per doubling of FGF23), CKD patients (β = 9.71), and non-CKD (β = 3.44)	< 0.05, < 0.0001	[137]
		Hemodialysis patients (125)	FGF23 was associated with left ventricular mass (54.615 ± 38.318 RU/mL vs. 35.070 ± 33.763 RU/mL)	0.003	[138]
		Elderly men and women (795)	FGF23 was positively associated with left ventricular mass index (β = 0.11), with increased OR for the presence of LVH (OR 1.28)	< 0.005, < 0.02	[139]
	OP	Hemodialysis patients (100)	Negative correlation of FGF23 with lumbar spine BMD ($r = -0.209$)	< 0.05	[143]
		CKD patients (81)	Negative correlation of FGF23 with lumbar spine BMD ($r = -0.25$)	< 0.05	[144]
		Hemodialysis patients (90)	FGF23 was increased in patients with OP (at lumbar site; 192.90 ± 242.32 vs. 428.13 ± 275.64 pg/mL)	< 0.05	[145]
		Hemodialysis patients (43)	Negative correlation of FGF23 with lumbar spine BMD (estimated effects from − 0.09 to − 0.12) and femoral neck BMD (− 0.06)	< 0.05	[146]

Table 2 (continued)

Cytokine	Disease	Subjects (*N*)	Relationships between the cytokine and the disease	*P* value	Ref.
		Hemodialysis patients (64)	FGF23 was increased in patients with OP (218.71 ± 28.62 vs. 296.18 ± 48.57 pg/mL)	< 0.05	[147]
		Hemodialysis patients (99)	No correlation between FGF23 and BMD	0.239	[148]
		CKD patients (131)	No association between FGF23 and BMD	0.821	[149]
		Hemodialysis patients (125)	No correlation between FGF23 and BMD	0.072	[150]
		Premenopausal, early and late postmenopausal women (180)	Negative correlation of FGF23 with lumbar spine BMD ($r = -0.813$) and proximal femur BMD ($r = -0.679$)	< 0.05	[151]
		Postmenopausal women (55)	FGF23 was associated with femoral neck BMD ($r^2 = 0.1$)	< 0.05	[152]
		Postmenopausal women (355)	No association between FGF23 and lumbar spine BMD	0.609	[153]
		Premenopausal women (2892)	FGF23 did not correlate with BMD	NS	[155]
		Older men (1329)	Higher total hip BMD (β = 0.02) per doubling of FGF23	0.04	[154]
		Older women (2008)	No significant relationship between 2-fold increases of FGF23 and total hip BMD	NS	[154]
		Elderly men (3014)	No association between FGF23 and BMD (adjusted for traditional confounding variables)	NS	[156]
		Older men (2868)	Higher risk of all fractures (+ 1.24 per SD increase of FGF23), vertebral fractures (+ 1.56), hip fractures (+ 2.18 in > 57.4 pg/mL of FGF23)	< 0.05, < 0.01	[157]
		Older men and women (2234)	The mean annualized % change in total hip BMD did not vary according to FGF23 quartile	0.7	[158]
		Older men and women (2786)	FGF23 was not associated with fracture risk	NS	[158]
		Men and women, data from GWAS - the ReproGen Alliance, GEFOS alliance, PheWAS databse, and MRC-IEU catalog	Decreased levels of heel BMD (β = − 0.201) and femoral neck BMD (β = − 0.286) were noted for every 1-unit increase in the log-transformed blood FGF23	0.016, 0.022	[159]
		Men and women, data from relevant GWAS, GEFOS, and UK Biobank	FGF23 was inversely associated with femoral neck BMD (OR 0.682) and heel BMD (OR 0.898)	< 0.001, 0.022	[160]
		Men and women (82) with OP	FGF23 was negatively correlated with relative bone volume ($r = -0.36$; $r = -0.29$) and trabecular number ($r = -0.28$; $r = -0.28$) at the distal radius and tibia, respectively	< 0.05, < 0.01	[161]
LCN2	T2DM	Lean women with normal glucose tolerance (11) and with T2DM (10)	LCN2 levels were elevated in T2DM patients (87.28 ± 5.1 ng/mL) versus lean healthy subjects (58.58 ± 7.61 ng/mL)	< 0.05	[181]
		Obese women with normal glucose tolerance (68) and with T2DM (48)	LCN2 levels were elevated in T2DM patients (83.5 ± 6.6 ng/mL) versus those with normal glucose tolerance (76.8 ± 9.2 ng/mL)	< 0.001	[182]
		Patients with T2DM (57) and non- diabetic controls (30)	LCN2 levels were increased in T2DM patients (87.68 ± 53.28 ng/mL) versus non-diabetics (45.32 ± 46.15 ng/mL)	0.001	[188]
		Adult T2DM patients (60) and healthy controls (30)	T2DM patients had higher levels of LCN2 (126.98 ± 14.31 ng/mL) than normal controls (75.86 ± 8.35 ng/mL)	< 0.001	[189]

Table 2 (continued)

Cytokine	Disease	Subjects (*N*)	Relationships between the cytokine and the disease	*P* value	Ref.
		Subjects with normal glucose tolerance (1143) and with T2DM (392)	LCN2 levels were elevated in T2DM patients (89.2 ± 8.3 ng/mL) versus those with normal glucose tolerance (69.2 ± 7.8 ng/mL)	< 0.001	[190]
		Subjects with normal glucose tolerance (142) and with T2DM (146)	LCN2 levels were increased in T2DM patients (166.54 ± 45.31 ng/mL) versus those with normal glucose tolerance (122.53 ± 26.15 ng/mL)	0.005	[191]
		Healthy men (25) and men with T2DM (30)	No association between LCN2 and T2DM (adjusted for WC)	0.88	[193]
		Healthy individuals (53) and T2DM patients (53)	LCN2 levels were decreased in T2DM patients (65.44 ± 8 ng/mL) vs. controls (98.2 ± 5.1 ng/mL)	< 0.001	[179]
	CVDs	Patients with coronary heart disease (49) and control subjects (42)	LCN2 levels were higher in patients with coronary heart disease (82.6 ± 38.7ng/mL) compared with the controls (43.8 ± 27.8ng/mL)	< 0.001	[185]
		Patients with acute heart failure (29) and without the event (159)	Patients with acute heart failure had increased levels of LCN2 than those without events (134 ng/mL vs. 84 ng/mL)	< 0.001	[196]
		Patients with acute coronary syndromes (87)	Plasma LCN2 was independent predictor of all cause mortality (OR 8.353)	0.0237	[197]
		Men with coronary artery disease (131) and control subjects (38)	Men with coronary artery disease had higher LCN2 levels (39.2 [29.3–56.5] ng/mL) than control subjects (32.7 [20.5–49.7] ng/mL)	< 0.05	[178]
		Men with developed CVDs (50) and men without CVDs (237)	LCN2 levels in men who developed CVD-related events were higher (21.0 [13.2–31.0] µg/L) than in men without CVDs (17.1 [11.9–24.5] µg/L)	0.012	[198]
		T2DM patients with subclinical atherosclerosis (78), control subjects (206)	Patients with subclinical atherosclerosis had increased LCN2 levels (112.9 [86.4 to 202.1] µg/L) than those without the event (77.2 [55.0–150.4] µg/L)	0.002	[199]
		T2DM patients with cardiac hypertrophy (30) and without cardiac hypertrophy (84)	Subjects with cardiac hypertrophy had higher levels of LCN2 (44.0 [38.3 – 50.6] ng/mL) than those without hypertrophy (36.0 [33.1–39.2] ng/mL)	0.017	[200]
		Cardiovascular mortality group (38), survivor group (102)	LCN2 levels were higher in the cardiovascular mortality group than in the survivor group (129 [79–625] µg/L vs. 117 [56–352] µg/L); LCN2 was independent predictor of mortality (OR 3.6)	< 0.01, 0.02	[201]
		Elderly patients with chronic heart failure (46) and healthy controls (number not shown)	LCN2 levels in the patient cohort were higher (458.5 [62.5–1212.4] ng/mL) than those in healthy age-balanced controls (37.8 [15.9–46.5] ng/mL)	< 0.001	[202]
		Subjects with cardiovascular mortality over 11 years (169) and survivor group (957)	LCN2 was a predictor of CVD mortality (HR 1.33 per SD log increase)	0.001	[203]
		Older women with coronary heart disease over 14.5 years (256) and those without the events (875)	A 35–37% increase in relative hazards for coronary heart disease (HR 1.29) per SD increase in LCN2	< 0.001	[204]
	OP	Healthy (44) and osteoporotic (29) men and women	No correlation between LCN2 and BMD in the spine and/or hip.	0.07	[206]
		Postmenopausal women with low BMD (120) and controls (55)	No difference in LCN2 levels between women with low BMD (T score below – 1.0) and control group	0.26	[207]
		Postmenopausal women with OP (43) and controls (31)	No difference in LCN2 levels between osteoporotic and control groups	NS	[208]
		Postmenopausal and premenopausal women with (161) and without (849) osteoporotic fractures	No difference in LCN2 concentrations between women with and without osteoporotic fractures (after adjusting for age)	NS	[209]
		Elderly women over 70 years (1009)	A 30% increase in the risk of any osteoporotic fracture (HR 1.30) per SD increase in LCN2 level	< 0.001	[210]

Table 2 (continued)

Cytokine	Disease	Subjects (*N*)	Relationships between the cytokine and the disease	*P* value	Ref.
SCL	T2DM	Adult patients (3015)	Positive association between SCL and T2DM (OR 1.23)	< 0.001	[231]
		Postmenopausal women with T2DM (265) and control group (225)	SCL levels were higher in diabetic group (48.2 ± 19.4 pmol/L) versus control (37.2 ± 18.6 pmol/L) and were increased with age in both groups	< 0.001	[233]
		Postmenopausal women with T2DM (40) and control group (40)	SCL levels were elevated in T2DM patients (53.18 ± 0.94 pmol/L) compared to controls (47.50 ± 12.62 pmol/L)	< 0.05	[234]
		Patients with T2DM (74) and control group (50)	SCL levels were higher in T2DM patients (54.56 ± 24.98 pmol/L) versus controls (42.11 ± 16.23 pmol/L)	< 0.001	[235]
		Patients with T2DM (40) and control group (62)	SCL levels were increased in T2DM patients (data displayed only in graphs)	< 0.001	[236]
		Men with T2DM (71) and control group (30)	Men with T2DM had higher SCL levels (59.2 ± 19.4 pg/mL) than healthy controls (45.2 ± 12.8 pg/mL)	< 0.001	[237]
		Postmenopausal women with T2DM (482) and control group (482)	SCL levels were higher in T2DM women versus control group (68.12 ± 14.15 vs. 41.22 ± 16.12 nmol/L)	< 0.001	[238]
		Postmenopausal women with T2DM (47) and older men with T2DM (72)	SCL levels were elevated in diabetic men (1.79 ± 0.69 ng/mL) than in women (1.10 ± 0.38 ng/mL); raising SCL levels were associated with an increased risk of vertebral fractures in T2DM patients	< 0.01	[239]
		Men and women (1778) with no history of T2DM	SCL was associated with fasting insulin ($\beta = -1.3 \times 10^{-3}$) and HOMA-IR ($\beta = -3.1 \times 10^{-3}$); no association was found with T2DM risk (HR 1.30).	< 0.001, NS	[240]
	CVDs	Older men with coronary artery calcification (57) and those without the disease (134)	Increased SCL levels (48.7 ± 12.8 pmol/L vs. 43.7 ± 16.5 pmol/L) were associated with a higher prevalence of coronary artery calcification (OR 1.61 per SD of SCL)	0.05	[244]
		Adult patients (2054)	Higher SCL was associated with elevated risk of death from heart disease (HR 1.13) and severity of coronary artery disease (β = 0.05)	0.007, 0.018	[231]
	OP	Postmenopausal patients with OP (480) and control group (170)	SCL levels were lower in patients with OP (38.79 ± 7.43 pmol/L) versus controls (52.86 ± 6.69 pmol/L) and positively correlated with lumbar spine BMD ($r = 0.391$)	< 0.001	[248]
		Postmenopausal osteoporotic patients (49) and control group (13)	SCL levels were decreased in postmenopausal patients with OP (37.4 ± 1.8 pmol/L) versus control (46.9 ± 2.9 pmol/L) and positively correlated with lumbar spine BMD ($r = 0.353$)	< 0.05, 0.005	[249]
		Men with idiopathic OP (116) and controls (116)	Men with idiopathic OP had lower SCL levels (0.54 ± 0.17 ng/mL) versus controls (0.66 ± 0.23 ng/mL); SCL levels dispayed a positive association with areal BMD (β = 0.267)	< 0.001, < 0.01	[250]
		Patients with postmenopausal OP (350) and controls (150)	Patients with postmenopausal OP had reduced SCL levels (38.40 ± 7.81 pmol/L) versus controls (53.02 ± 6.83 pmol/L)	< 0.001	[251]
		Kidney transplant patients with OP (34) and those without OP (44)	Patients with OP had lower SCL (405.9 ± 234.9 ng/dL) levels than those from non-osteoporotic group (521.7 ± 233.5 ng/dL)	< 0.05	[252]
		Postmenopausal women (572)	Serum SCL correlated positively with spine ($r = 0.35$) and total hip ($r = 0.25$) BMD	< 0.0001	[253]
		Men and women (170), 30–90 years	SCL levels were decreased in OP (4.62 ± 1.6 ng/mL) and osteopenia (4.92 ± 1.4 ng/mL) compared with controls (5.74 ± 1.3 ng/mL)	< 0.0001	[254]

Table 2 (continued)

Cytokine	Disease	Subjects (*N*)	Relationships between the cytokine and the disease	*P* value	Ref.
		Women with postmenopausal OP (60) and those without OP (60)	Patients with postmenopausal OP had higher SCL levels (26.65 ± 37.77 pmol/L) versus controls (22.8 ± 34.10 pmol/L)	< 0.05	[255]
		Patients with osteoporotic fractures (103) and subjects without fractures (103)	SCL levels were lower in patients with osteoporotic fractures (1.21 ng/mL) compared to those without fractures (1.36 ng/mL); SCL was positively related to BMD at all skeletal sites	< 0.05	[257]
		Osteoporotic fracture patients (46) and non- osteoporotic fracture patients (133)	Osteoporotic fracture patients had reduced SCL levels (41.9 ± 14.4 pmol/L) compared to non-osteoporotic fracture ones (48.1 ± 17.5 pmol/L); SCL was positively associated with BMD ($r = 0.17$)	0.03, 0.026	[258]
		Elderly patients with hip fracture (89) and healthy controls (82)	SCL levels did not differ between patients with a fracture and controls	0.44	[259]
		Postmenopausal women with OP-related fractures (138) and those without fractures (569)	SCL was positively correlated with a fracture risk (HR 7.94 for increase of 1 SD in SCL level) at follow-up period of 5.2 years	< 0.05	[260]
		Older women with hip fractures (228) and controls (204)	Hip fracture risk increased by 51% (HR 1.51) for an increase of 1 SD in SCL level at follow-up period of 9.8 years; total hip BMD correlated with SCL concentrations ($r = 0.27$)	< 0.05, < 0.001	[261]

BMD bone mineral density, *CACS* coronary artery calcification score, *CKD* chronic kidney disease, *CVDs* cardiovascular diseases, *FDR* false discovery rate, *FGF23* fibroblast growth factor 23, *GWAS* genome-wide association studies, *HOMA-IR* homeostatic model assessment for insulin resistance, *HR* hazard ratio, *LCN2* lipocalin 2, *LVH* left ventricular hypertrophy, *OP* osteoporosis, *OR* odds ratio, *r* correlation coefficient, *SCL* sclerostin, *SD* standard deviation, *T2DM* type 2 diabetes mellitus, *WC* waist circumference

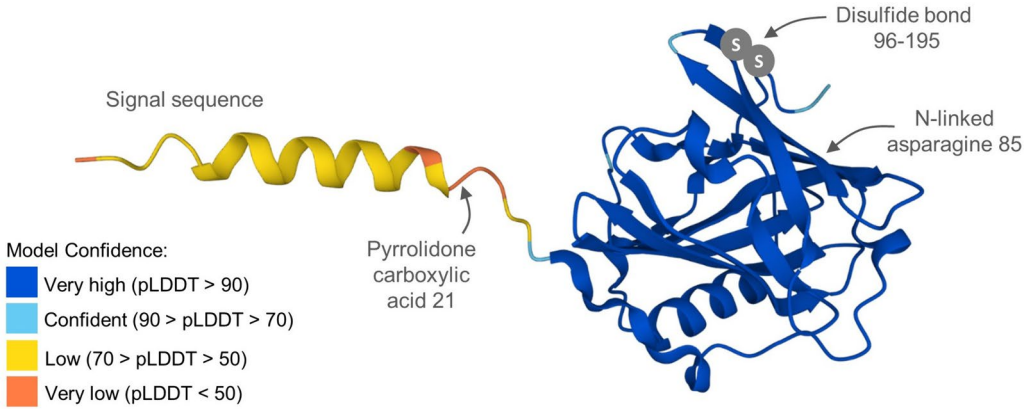

Fig. 3 Human LCN2 structure prediction according to AlphaFold Protein Structure Database (RRID: SCR_023662; [264, 265]). 3D visualization of LCN2 structure prediction with colored per-residue confidence metric (pLDDT) is shown. Positions of glycosylation, modified residue, and disulfide bond on LCN2 molecule are illustrated according to the database UniProt (RRID: SCR_002380)

numerous cells, e.g. osteoblasts [95, 165], immune cells, adipocytes, hepatocytes, renal cells [162], chondrocytes [166]; as well as by bone marrow, thymus, small intestine [162], spleen, muscles [167].

LCN2 plays a key role in various biological processes, such as iron (Fe) and fatty acids delivery, metabolic homeostasis, apoptosis of hematopoietic cells [166], cell proliferation [168], organogenesis [169], and modulation of inflammation [170]. Interestingly, LCN2 expression is upregulated in numerous diseases, e.g. various cancers [171–173], cardiomyopathies [174], CKD [175], liver disease [176].

It was reported that higher circulating levels of LCN2 were associated with an increased risk of MetS in older women. Women in the highest LCN2 quartile had approximately three times greater risk of MetS compared to those in the lowest quartile [177]. Elevated levels of LCN2 were observed in men versus women [178, 179]. In addition, LCN2 levels were higher in men with MetS compared to non-MetS subjects and showed a positive correlation with the number of MetS components [178]. Most studies demonstrated a close relationship between LCN2 levels and obesity. A positive correlation between circulating LCN2, BMI, and WC was found in lean as well as overweight/obese individuals [180], prediabetic women [181], and men [178]. LCN2 was correlated with BMI in healthy individuals [179], obese women [182], and T2DM patients [183]. On the other hand, no significant correlation between LCN2 levels and BMI or WC was reported in healthy men [184] and patients with coronary heart disease [185]. According to Mosialou et al. [181, 186], LCN2 suppresses appetite in a melanocortin 4 receptor-dependent manner. LCN2 upregulation may serve as a protective mechanism to combat obesity-induced glucose intolerance by reducing food intake and promoting adaptive β-cell proliferation. The regulatory importance of LCN2 may be associated with the stimulation of PPARγ, which mediates adipogenesis and lipogenesis in liver and adipose tissues.

Positive correlations between TGs and LCN2 levels were reported in obese women, healthy women and men, T2DM patients and those underwent coronary angiography [177–180, 182, 183]. However, in healthy men [184] and patients with coronary heart disease [185], LCN2 did not correlate with TGs. On the other hand, circulating LCN2 was negatively correlated with HDL cholesterol [177, 179, 180, 182–185]. In studies by Park and Choi [187] and Zhang et al. [183], LCN2 concentrations positively correlated with systolic and diastolic blood pressures. Some researches [180, 182] revealed a positive correlation between LCN2 and systolic blood pressure but not diastolic blood pressure. Conversely, several studies [177, 184, 185] found no correlation between LCN2 levels and blood pressure.

In most clinical studies [181, 182, 188–191], significantly higher LCN2 levels were determined in T2DM patients, as LCN2 expression is increased after the onset of hyperglycemia and is stimulated by insulin in the glucose- and NFκB-dependent manner [192]. On the contrary, findings by De la Chesnaye et al. [179] showed decreased LCN2 levels in patients suffering from T2DM. Al-Absi et al. [193] identified no significant differences in LCN2 between T2DM men and their controls.

Regarding CVDs, LCN2 is highly expressed in cardiomyocytes and atherosclerotic plaques [194, 195]. Therefore, elevated LCN2 levels were recorded in patients with coronary heart disease [185], acute heart failure and acute coronary syndromes [196, 197]. According to Ni et al. [178], males with coronary artery disease had higher LCN2 levels versus controls, whereas females did not.

Similarly, increased levels of LCN2 were found in men with CVD-related events but not in women [198]. These sex-dependent differences can be explained by the interrelationship between LCN2 levels, estrogens and their effects, as LCN2 influences estradiol biosynthesis and estrogen receptor signaling. Increased circulating LCN2 levels were also determined in T2DM patients with subclinical atherosclerosis and positive correlations were observed also between LCN2 and carotid and femoral intima-media thickness [199]. In addition, higher levels of LCN2 were recorded in T2DM patients with cardiac hypertrophy [200]. Some clinical observations and follow-up studies suggest that LCN2 may have an important prognostic value in survival assessment. Circulating LCN2 predicted cardiovascular mortality in patients after cerebrovascular ischemia [201], those with chronic heart failure [202], as well as in older adults [203, 204].

LCN2 is expressed by osteoblasts at ten-fold higher levels than in white adipose tissue or other organs [186]. Additionally, LCN2 has been identified as essential for normal osteogenic differentiation of mesenchymal stem cells, but its overexpression and oversecretion inhibited osteogenic differentiation of these cells [205]. Clinical studies found no association between LCN2 levels and BMD in postmenopausal women with OP [206–208]. No significant differences in LCN2 concentrations were noted between patients with and without fracture in postmenopausal as well as premenopausal women [209]. On the other hand, a prospective study in a cohort of elderly women demonstrated that high levels of circulating LCN2 predicted future risk of OP-related fractures [210]. These findings are consistent with observations in transgenic mice overexpressing LCN2, where changes in bone microarchitecture were linked to bone fragility [211]. Moreover, according to Rucci et al. [212], LCN2 could be involved in the onset of OP in the presence of mechanical constraints such as inactivity, bed rest, muscle damage or aging. The mechanisms of LCN2 action could include a decrease in osteoblast differentiation and an increase in osteoblast-induced osteoclastogenesis. It could also affect osteoblasts through the modulation of energy metabolism [213].

Summarizing the aforementioned information, it can be stated that higher levels of LCN2 are positively correlated with the number of MetS components. In addition, LCN2 levels are higher in individuals with obesity, T2DM, and CVDs. In obese subjects, a positive correlation was found between circulating LCN2, BMI, WC, and TGs. Conversely, circulating LCN2 was negatively correlated with HDL cholesterol. Elevated levels of LCN2 have been found in T2DM patients, T2DM subjects with subclinical atherosclerosis, patients with coronary heart disease, acute heart failure, and acute coronary syndromes. However, most clinical studies showed no association between LCN2 levels and BMD in individuals with OP. Circulating LCN2 can also be used as a promising predictor for cardiovascular mortality in patients after cerebrovascular ischemia, those with chronic heart failure, as well as in older adults.

Links among sclerostin, metabolic syndrome, and the most common metabolic syndrome-related diseases affecting bone quality

Sclerostin (SCL) is secreted by osteocytes and plays an important role in the development and maintenance of bone tissue [214]. It is primarily synthesized as a 24 kDa and 213 amino acid-long glycoprotein with a signal peptide comprising the first 23 amino acids. The circulating form of SCL is a 190-residue glycoprotein with a molecular weight of 22 kDa, which is formed by cleavage of the signal peptide (Fig. 4). SCL is encoded by the *SOST* gene, which is located on the chromosomal region 17q12-21 in humans [215]. Human SOST mRNA is expressed in the heart, aorta, liver, and kidneys [216]. SCL as a potent inhibitor of osteoblastogenesis, binds to the Wnt co-receptors of the low-density lipoprotein receptor-related protein (LRP) family, LRP5 and LRP6, antagonizing downstream signaling. In addition, SCL via inhibition of Wnt signaling pathway has a potential to stimulate osteoclast differentiation and enhance bone resorption [217]. It has been reported that this bone-derived cytokine may have a potential role in extra-skeletal tissue as well [214]. Recent studies [218, 219] have highlighted an important role of SCL in myogenesis, where SCL inhibits myoblast differentiation, thereby modulating bone-muscle interaction.

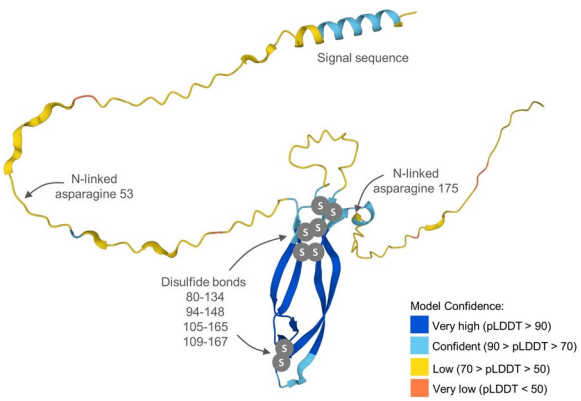

Fig. 4 Human SCL structure prediction according to AlphaFold Protein Structure Database (RRID: SCR_023662; [264, 265]). 3D visualization of SCL structure prediction with colored per-residue confidence metric (pLDDT) is shown. Positions of glycosylation and disulfide bonds on the SCL molecule are illustrated according to the database UniProt (RRID: SCR_002380)

In general, serum SCL was higher in older men with MetS and its level increased significantly across the elevating number of MetS components. A positive correlation between SCL level and WC was recorded. However, this correlation lost significance after correction for whole-body bone mineral content (BMC) [220]. Accumulating evidence has revealed an association between circulating SCL and obesity. According to Ma et al. [221], SCL levels were related to higher total fat mass (FM) and vertebral bone marrow fat in older men but not in women. On the contrary, Urano et al. [222] stated that SCL levels were positively associated with FM and strongly correlated with LDL cholesterol and homocysteine in postmenopausal women. In addition, high SCL levels were determined in obese patients and they decreased significantly after laparoscopic sleeve gastrectomy [223, 224]. On the contrary, Azzam et al. [225] revealed lower SCL levels in obese individuals compared to overweight and control groups; however, these groups included low numbers of individuals. Furthermore, FM was one of the most important predictors of SCL level in adolescent females with increased physical activity [226]. Moreover, circulating SCL declined in response to moderate-intensity exercise training in older adults [227]. According to Kurgan et al. [228], subcutaneous adipose tissue SCL was reduced and Wnt signaling was enhanced after four weeks of interval sprint training in young obese men, suggesting a role of SCL in regulating adipose tissue in response to exercise. Finally, mutations in LRP5, particularly those affecting the interaction of SCL with this Wnt coreceptor [229], were associated with altered fat distribution [230]. Frysz et al. [231] found that SCL was positively associated with TGs and hypertension. Conversely, higher SCL was linked to lower HDL cholesterol. Bovijn et al. [232] examined BMD-increasing alleles in the *SOST* locus (as a proxy for SCL inhibition) and determined their association with higher risk of hypertension, systolic blood pressure, and TGs.

Considering T2DM, most studies reported higher SCL levels in T2DM patients and showed their positive correlations with BMI and age in both diabetic and healthy subjects [233–238]. Interestingly, if gender was taken into account, men with T2DM had increased SCL levels than women with T2DM [235, 236, 239], and this fact was associated with elevated risk of vertebral fractures [239]. On the other hand, findings from a cohort study by Yu et al. [240] showed that SCL levels were not strongly linked to T2DM risk, despite higher SCL levels in T2DM patients. Consistent with several studies, SCL levels were higher in individuals with impaired glucose regulation than in subjects with normal glucose tolerance. Furthermore, SCL levels positively correlated with fasting blood glucose and insulin resistance [241–243].

Recent studies have shown the importance of SCL in CVD-related events. Higher SCL levels were consistent with prevalence and extent of coronary artery calcification in older men [244]. According to Frysz et al. [231], SCL levels appear to be positively associated with coronary artery disease severity and mortality, which can be partially explained by the relationship between higher SCL levels and major CVD risk factors. Inhibition of SCL may be a therapeutic approach to reduce fracture risk in patients with OP. However, in this context, SCL lowering can increase the risk of myocardial infarction, the extent of coronary artery calcification, hypertension, and T2DM [245, 246]. Therefore, the use of romosozumab, a humanized anti-SCL monoclonal antibody, is not recommended for women at high risk of CVDs, particularly those who have had recent heart attacks or strokes [247]. Similarly, Bovijn et al. [232] reported an increased risk of CVD-related events after SCL inhibition. In their study, the *SOST* genetic variants were associated with a lower risk of fractures and OP, but with a higher risk of myocardial infarction and/or coronary revascularization, central adiposity, elevated systolic blood pressure, and T2DM.

In the majority of studies, lower SCL levels were determined in patients with OP [248–254]. Only Suarjana et al. [255] identified higher SCL levels in postmenopausal women with OP. The positive association between SCL and BMD suggests that serum SCL may reflect the number of SCL-secreting osteocytes, being reduced in patients with OP [256]. Moreover, higher mechanical strains in bones with lower BMD are also associated with decreased SCL levels [257]. Regarding SCL levels and the occurrence of OP fractures, Lim et al. [257] and Gorter et al. [258] found that patients with OP fractures had lower SCL levels than those without or non-OP fractures. Wanby et al. [259] did not find any difference in SCL level between patients with hip fracture and control group; however, much older individuals (over 75 years) were included in this study. On the other hand, considering the risk for OP-related fractures, two large prospective studies [260, 261] revealed that high levels of SCL may serve as a strong and independent risk factor for OP-related fractures in postmenopausal women. In this case, associations between SCL levels and fracture risk were independent of BMD and/or hip fracture risk was enhanced when high SCL levels were combined with lower BMD. However, these findings were strongly supported by the application of the SCL inhibitor romosozumab, which demonstrated that lowering SCL resulted in a reduction in fracture risk (by 73% and 36% for vertebral and clinical fractures, respectively) and an increase in BMD (by 13.3% in lumbar spine BMD) after one year of the therapy [262, 263]. The exact mechanism linking SCL levels and OP-related fracture risk is not clear, but it appears

to be related to SCL-induced inhibition of Wnt signaling pathway and subsequent decreased bone formation and increased bone resorption [260].

The information presented in this chapter shows that higher levels of SCL are reported in individuals with obesity, T2DM, and CVDs. In obese subjects, SCL levels are positively associated with FM, TGs, hypertension and show a decreasing trend in response to moderate or increased physical activity. In addition, circulating SCL appears to be positively related to coronary artery disease severity and mortality. On the other hand, higher SCL is associated with lower HDL cholesterol. Considering T2DM, SCL levels are elevated in patients with impaired glucose regulation and positively correlate with fasting blood glucose and insulin resistance. In patients with OP, reduced SCL levels are recorded.

Conclusion

Recent research demonstrates diverse functions of bone-derived cytokines and suggests their involvement in MetS. In fact, each component of MetS clearly affects bone mass and bone metabolism. In addition, MetS is associated with other serious disorders, including T2DM, CVDs, OP, which have an unfavorable impact on bone quality. Based on current studies, FGF23 may become useful biomarker for obesity, T2DM, and CVDs, as FGF23 levels were elevated in patients suffering from these diseases. In addition, FGF23 can be used as a predictive factor to evaluate the progression of CKD. LCN2 could serve as an indicator of obesity, dyslipidemia, T2DM, and CVDs. The levels of LCN2 positively correlated with obesity indicators, TGs, and negatively correlated with HDL cholesterol. Moreover, patients with T2DM and CVDs had increased LCN2 levels. Circulating LCN2 can also be used as a promising predictor related to cardiovascular mortality. SCL may act as a potential biomarker predicting the occurence of MetS including all its components, T2DM, CVDs, and OP. In contrast to LCN2, a positive association with hypertension was recorded for SCL. Higher levels of SCL were noted in subjects with T2DM, CVDs and lower in patients with OP. In conclusion, we can state that aforementioned bone-derived cytokines are involved in the outcomes of MetS, T2DM, CVDs, and OP. Therefore, they have the potential to serve as hopeful predictors and possible treatment targets in these diseases. However, further research on the endocrine system through bone-derived cytokines is needed, which may reveal new insights into the prediction, prevention, and treatment of MetS and MetS-related diseases negatively affecting bone quality.

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MM and RO were responsible for conceptualization, methodology, supervision, visualization, writing—original draft, writing—review & editing, and funding acquisition. VM, VK, MB, and NZ performed the literature search and data analysis. RB and NP were responsible for formal analysis. All authors read and approved the final manuscript.

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