Chapter 8
Bone as an Endocrine Organ: Diabetic Bone Disease as a Cause of Endocrine Disorder via Osteocalcin, FGF23 Secreted from Osteocyte/Osteoblast

Koichiro Yoda

Abstract Endocrine effects occur when organs secrete humoral physiologically active substances into the blood or other bodily fluids, and these active substances exert their physiological activities in target tissues. Fibroblast growth factor (FGF) 23, which is secreted by osteocytes, acts on the renal tubule and is involved in phosphorus metabolism. Osteocalcin, which is secreted by osteoblasts, acts on pancreatic β-cells and adipocytes and plays a role in insulin secretion and glycometabolism, in addition to its conventional role as a bone matrix protein. Thus, FGF23 and osteocalcin secreted from bone tissues function as endocrine hormones. Osteocyte and osteoblast functions are decreased in diabetes. Consequently, the secretion of FGF23 and osteocalcin is hindered. The decreased function of FGF23 causes hyperphosphatemia and leads to the progression of arteriosclerosis. The decreased function of osteocalcin results in decreased insulin secretion and increased insulin resistance. In this article, we describe the role of bone as an endocrine organ and its association with diabetes.

Keywords Undercarboxylated osteocalcin (ucOC) • Fibroblast growth factor 23 (FGF23) • Diabetes • Atherosclerosis • Hyperphosphatemia

8.1 FGF23

8.1.1 Overview

FGF23 is a 251-amino acid endocrine hormone produced primarily in osteoblasts/osteocytes. This hormone is encoded by the FGF23 gene, which was identified as a causal gene in a linkage analysis of families with a history of autosomal dominant hypophosphatemic rickets or osteomalacia. FGF23 belongs to the FGF13

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subfamily, which includes other structurally related homologues, FGF19 and FGF21. FGF23 is found in the serum of healthy people at a concentration of several tens of pg/mL. It regulates phosphorus metabolism, facilitates phosphorus excretion in the renal tubule, and further reduces phosphorus absorption from the digestive tract by suppressing the activity of vitamin D3 [$1,25(OH)_2D_3$]. As the functions of osteocytes and osteoblasts decrease in diabetes, FGF23 secretion resulting from phosphorus loading decreases, and serum phosphorus levels increase after meals. In chronic renal failure, in which the urinary secretion of phosphorus is decreased, the FGF23 level starts to increase when the glomerular filtration rate reaches approximately 60 mL/min. This is prior to PTH, which plays a similar role in the urinary secretion of phosphorus. Decreased FGF23 secretion facilitates the stimulation of bone metabolism turnover caused by the increase in PTH, resulting in the stimulation of Ca recruitment to blood from bone. This increased serum phosphorus or Ca level can be a risk factor for Monckeberg medial calcific sclerosis, a characteristic feature of patients with diabetes or chronic renal failure. In summary, decreased FGF23 function is associated with arteriosclerosis progression, cardiovascular events, and an increase in the mortality rate.

8.1.2 Localization

FGF23 is considered to be mainly located within bone tissues in vivo. The expression of FGF23 mRNA increases in a concentration-dependent manner in human osteoblast-like cells in response to increased levels of extracellular phosphate [1]. Furthermore, elevated FGF23 expression in osteocytes and osteoblasts has been confirmed in a murine model of X-linked dominant hypophosphatemic rickets, in which FGF23 is overexpressed due to an abnormality in the phosphate-regulating gene with homologies to endopeptidase on the X chromosome (PHEX) gene [2]. Functions of FGF23-producing osteocytes and osteoblasts decrease in diabetes (Fig. 8.1). Mesenchymal stem cells normally differentiate into osteocytes

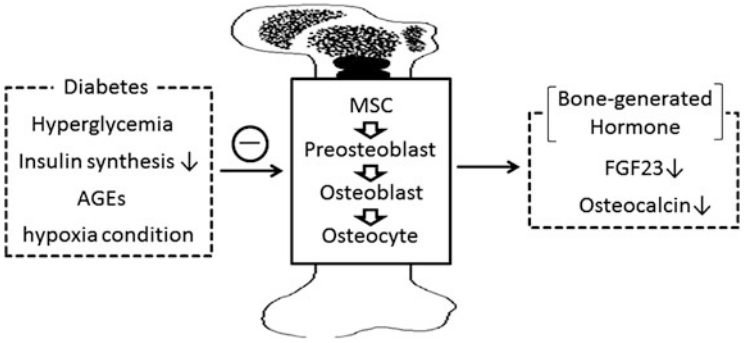

Fig. 8.1 Diabetes and bone-generated hormone interaction via osteoblast/osteocyte impairment. Several factors associated with diabetes impair osteoblast/osteocyte differentiation and function where FGF23 and osteocalcin were generated. *AGEs* advanced glycation end products, *MSC* mesenchymal stem cell

via preosteoblasts, immature osteoblasts, and mature osteoblasts. The differentiation of osteoblasts is inhibited by conditions commonly found in diabetes, such as hyperglycemia, impaired insulin function, and decreased blood flow to bones that accompanies microangiopathy. Hyperglycemia is directly toxic to osteoblasts themselves. Acute hyperglycemia and its associated hyperosmolality suppress the expression of genes involved in osteoblast maturation [3]. High blood glucose leads to the enhanced formation and accumulation of advanced glycation end products (AGEs) in bone. It has been shown that AGEs stimulate osteoblast apoptosis [4]. Hyperglycemia and oxidative stress may also affect mesenchymal stem cell differentiation. Culturing mesenchymal stem cells in high glucose media reduced the levels of osteoplastic markers such as osteocalcin and osteopontin [5]. Diabetes is also linked to generalized damage of blood vessel walls, which results in micro- and macrovascular complications. Oxygen tension within the marrow microenvironment is physiologically lower than that in other tissues, and the presence of diabetes may further alter cellular homeostasis. Indeed, it has been reported that differentiation of mesenchymal stem cells toward either the adipose or osteoblast phenotypes is reduced under hypoxic conditions [6].

8.1.3 Regulation of Phosphorus Metabolism

Serum phosphorus levels are mainly regulated by phosphorus absorption from the digestive tract and phosphorus reabsorption in the renal tubule (Fig. 8.2). Most of the phosphorus filtered in the glomerulus is reabsorbed in the proximal renal tubule. Type 2a and 2c sodium–phosphate cotransporters are responsible for the physiological reabsorption of phosphorus in the proximal renal tubule. FGF23 acts on the Klotho–FGF receptor (FGFR) complex in the renal tubule and suppresses phosphorus reabsorption by decreasing the expression of type 2a and 2c sodium–phosphate cotransporters [7]. In the kidney of streptozotocin-induced diabetic rats, decrease of Klotho and FGFR expression by high glucose has been documented [8]. FGF23 also decreases the level of activated vitamin D3 [1,25 $(OH)_2D_3$], which accelerates phosphorous absorption from the digestive tract, by decreasing the expression of Cyp27b1 (1α-hydroxylase), an enzyme producing 1,25 $(OH)_2D_3$, and by facilitating the expression of Cyp24 (24-hydroxylase), which transforms $1,25(OH)_2D_3$ into a metabolite with lower activity [9]. As shown above, FGF23 decreases serum phosphorus levels by suppressing phosphorus reabsorption in the renal tubule as well as phosphorus absorption from the digestive tract by decreasing the serum $1,25(OH)_2D_3$ level.

We previously reported a decrease in FGF23 responsiveness to phosphorus loading in patients with diabetes (Fig. 8.3) [10]. Phosphorus (1 g) was orally administered to patients with type 2 diabetes ($n = 10$) and nondiabetic patients ($n = 10$), and then, the short-term effect was examined. Patients in both groups

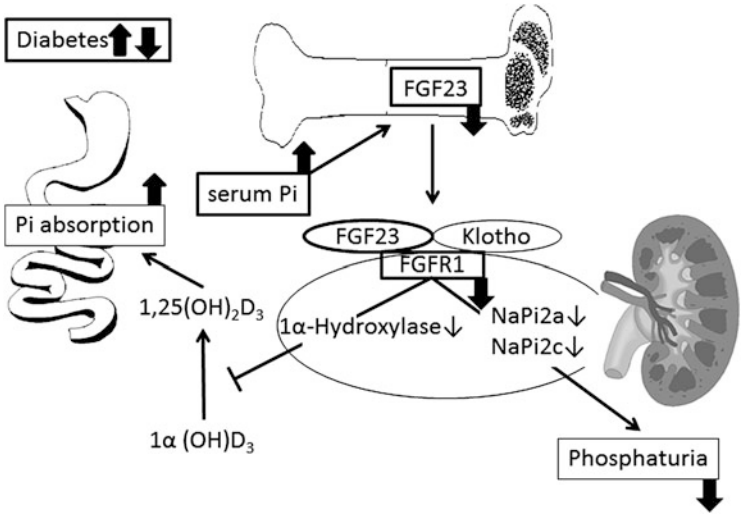

Fig. 8.2 Possible influence of diabetes on the regulation and action of FGF23. Increased serum Pi causes FGF23 to be released from skeletal osteoblasts/osteocytes. The major known effects of FGF23 are inhibition of Na–Pi cotransport in the kidney and the resultant phosphaturia and inhibition of 1α(OH)D3 hydroxylase, which reduces levels of activated vitamin D3 [1,25 $(OH)_2D_3$]. Reduced 1,25$(OH)_2D_3$ levels decrease gastrointestinal Pi absorption. In diabetes, impaired production of FGF23 at osteoblasts/osteocytes and downregulation of FGF23-specific receptor that is composed of Klotho and FGF receptor 1 (FGFR1) may lead to decrement in phosphaturia and increment in Pi absorption

were confirmed to have no renal dysfunction. The serum FGF23 level was significantly increased in the nondiabetic group 2 and 4 h after the administration of phosphorus, whereas no increase was observed in the diabetic group. The serum iPTH level also increased significantly in the nondiabetic group 4 h after the load, whereas no increase was seen in the diabetic group. Serum phosphorus levels were significantly increased in both groups 2 h after phosphorus administration. Although the serum phosphorus level continued to increase in the diabetic group up to 4 h after the administration, it was suppressed in the nondiabetic group. Next, the long-term effect of phosphorus loading was examined by administering phosphorus (2 g per day) orally on two consecutive days. Significant increases in both serum FGF23 and iPTH levels were observed only in the nondiabetic group 3 days after the administration. When phosphorus was orally administered for 7 days to patients with chronic renal failure, the serum FGF23 level continued to increase from the basal value in the nondiabetic group during the investigation, whereas no such change was seen in the diabetic group [11].

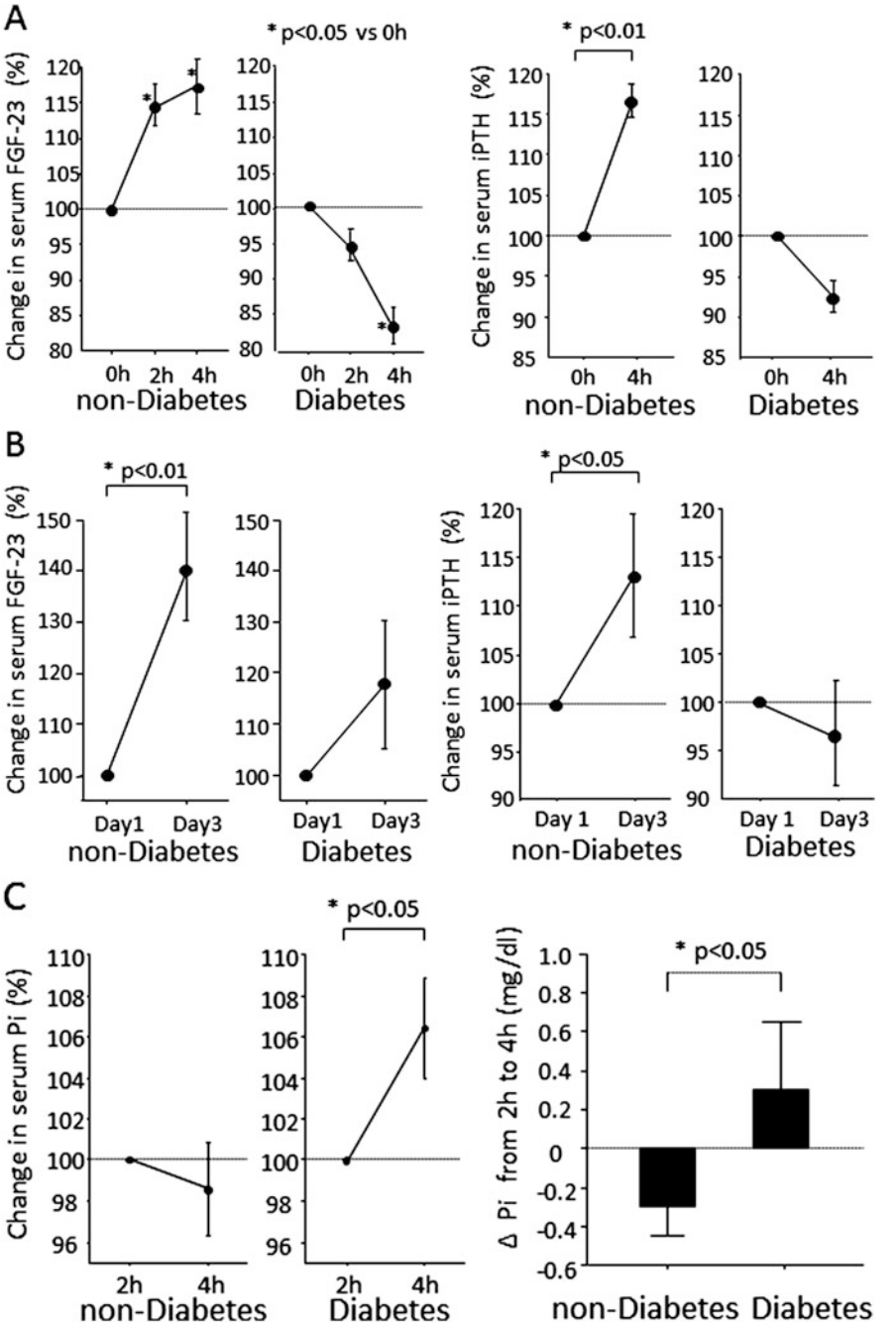

Fig. 8.3 Impaired responses of serum FGF23 and iPTH to oral Pi stimulation test. (**a**) Time courses of serum FGF23 and iPTH from 0 to 4 h after intake of Pi on day 1. In nondiabetic patients, serum FGF23 elevated significantly ($P = 0.046$ by ANOVA) and showed a significant increase at 2 h after Pi stimulation ($P < 0.05$ by Fisher test). In contrast, serum FGF23 was significantly reduced in diabetic patients ($P = 0.018$ by ANOVA) and showed a significant decrease at 4 h

8.1.4 Association with Arteriosclerosis

Because an increase in the serum phosphorus level is a risk factor for cardiovascular calcification and reduced life expectancy, the serum FGF23 level, which decreases the serum phosphorus level, helps predict the onset of cardiovascular calcification and reduced life expectancy. Chronic renal failure is one of the pathological conditions in which the serum phosphorus level is increased. When renal function decreases, this phosphaturic effect is hindered, and phosphorus accumulates in the body. In chronic renal failure, FGF23 increases when the estimated glomerular filtration rate reaches around 60 mL/min, which is before PTH [12], and this protects against an increase in the serum phosphorus level. For this reason, the FGF23 increase is a predictive factor for the progression of chronic renal failure, which is independent of the amount of albumin excreted into the urine [13]. When renal failure reaches the advanced stage, FGF23 levels are progressively increased to compensate for persistent phosphate retention, but this results in reduced renal production of activated vitamin D and decreased serum Ca and leads to secondary hyperparathyroidism (Fig. 8.4). As a result, Ca and phosphorus are recruited from bone to blood and increase the risk of cardiovascular calcification. Vessel calcification caused by this mechanism is called Monckeberg medial calcific sclerosis to distinguish it from the atherosclerotic plaques in the vascular intima. It is characterized by calcification within the vascular media. Increased areas of Monckeberg calcification are involved in the onset of cardiovascular events and the increase in the mortality rate [14]. The frequency of Monckeberg calcification in the peripheral artery (the artery in the hand) [15] and in the abdominal artery [16] reportedly increases in diabetic patients compared with nondiabetic patients. This suggests diabetes is a state where it is easy to accumulate phosphate and leads to secondary hyperparathyroidism. Based on this background, the increase in serum FGF23 can serve as a predictive factor for total death, in addition to cardiovascular events, in patients with chronic renal failure [17] or in patients on dialysis [18].

Some studies have suggested the direct involvement of FGF23 in the progression of vascular calcification, in addition to its indirect involvement via phosphorus metabolism. The FGF23 signal is transmitted through its binding to the Klotho–FGFR complex, which consists of membrane-bound Klotho and FGFR-1 and FGFR-3. Lim et al. reported that the Klotho–FGFR complex was expressed not

Fig. 8.3 (continued) ($P < 0.05$ by Fisher test). During oral Pi stimulation, serum iPTH significantly increased from 0 to 4 h in nondiabetic patients ($P = 0.007$) but not in diabetic patients ($P = 0.072$). (**b**) Comparison of serum FGF23 and iPTH levels on day 1 (0 h) and day 3 (0 h). An oral Pi load for 2 days significantly increased serum FGF23 and iPTH in nondiabetic patients ($P = 0.009$, $P = 0.048$) but not in diabetic patients ($P = 0.241$, $P = 0.507$). (**c**) Comparison of serum Pi changes in nondiabetic and diabetic patients. Serum Pi significantly increased between 2 and 4 h in diabetic patients ($P = 0.020$), whereas there was no significant change in nondiabetic patients ($P = 0.574$). The serum Pi changes from 2 to 4 h differed significantly between the two groups ($P = 0.027$)

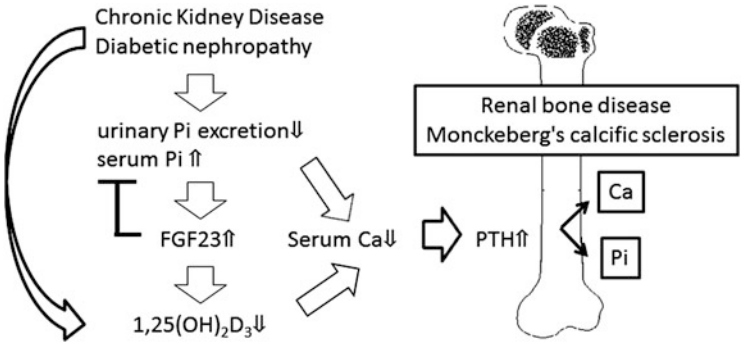

Fig. 8.4 The role of FGF23 in chronic kidney disease – mineral and bone disorder. In patients with chronic kidney disease, circulating FGF23 levels are progressively increased to compensate for persistent phosphate retention, but this results in reduced renal production of activated vitamin D3 [$1,25(OH)_2D_3$] and leads to secondary hyperparathyroidism. Ca and Pi are recruited from bone to blood and increase the risk of cardiovascular calcification known as Monckeberg calcific sclerosis

only in the renal tubule but also in the arteries of healthy people [19]. When examined in arterial smooth muscle cells, the sensitivity of the Klotho–FGFR complex toward FGF23 decreased, and the calcification of vascular media was accelerated under the condition of high glucose and/or uremia. Even in clinical trials, the decrease in FGF23 was reported to be a risk factor, independent of the increase in the Ca/phosphorus product, of the calcification of peripheral arteries [20] and the arch aorta [21], and these reports support the direct involvement of FGF23 in suppressing vascular calcification.

8.2 Osteocalcin

8.2.1 Overview

Osteocalcin was identified as a bone matrix protein mainly secreted by osteoblasts. Osteocalcin is carboxylated by γ-carboxylase, and most of it is embedded within the bone as part of the bone matrix. In blood, osteocalcin exists in the following two forms: one with all three glutamic acid residues carboxylated and the other with less carboxylation of the residues. Undercarboxylated osteocalcin (ucOC) facilitates the synthesis and secretion of insulin in the pancreas and increases the insulin sensitivity of peripheral tissues. In addition, insulin signaling in osteoblasts activates osteocalcin by regulating the interaction between osteoblasts and osteoclasts. In this manner, bone tissue creates a positive feedback mechanism that acts on pancreatic β-cells and adipose tissues via hormones such as ucOC and insulin. Some reports on clinical studies in humans have also suggested that ucOC facilitates insulin secretion and enhances insulin sensitivity.

8.2.2 *Feedback Mechanism of Insulin and ucOC (Fig. 8.5)*

In murine research, insulin directly acts on osteoblasts to facilitate osteocalcin synthesis [22]. Furthermore, it inhibits the synthesis of osteoprotegerin (OPG), which has a suppressive effect on osteoclast differentiation factor (RANKL) [23]. Osteocalcin synthesized in osteoblasts is further modified with the addition of a carbonate ion to a γ-glutamic acid residue by vitamin K-dependent carboxylase, which is then secreted as γ-carboxylated osteocalcin (cOC) [24]. cOC binds to hydroxyapatite within the bone matrix and accumulates in bone tissues. Meanwhile, because a decrease in OPG secretion enhances the function of RANKL, osteoclast formation is facilitated. As a result, bone resorption by osteoclasts is stimulated. Proton (H^+) and chloride ions (Cl^-) are secreted from the ruffled borders of osteoclasts into resorption cavities to form an acidic environment, which leads to the decalcification of bone minerals. In such an acidic environment, cOC bound to hydroxyapatite undergoes decarboxylation to yield ucOC, which is released into the

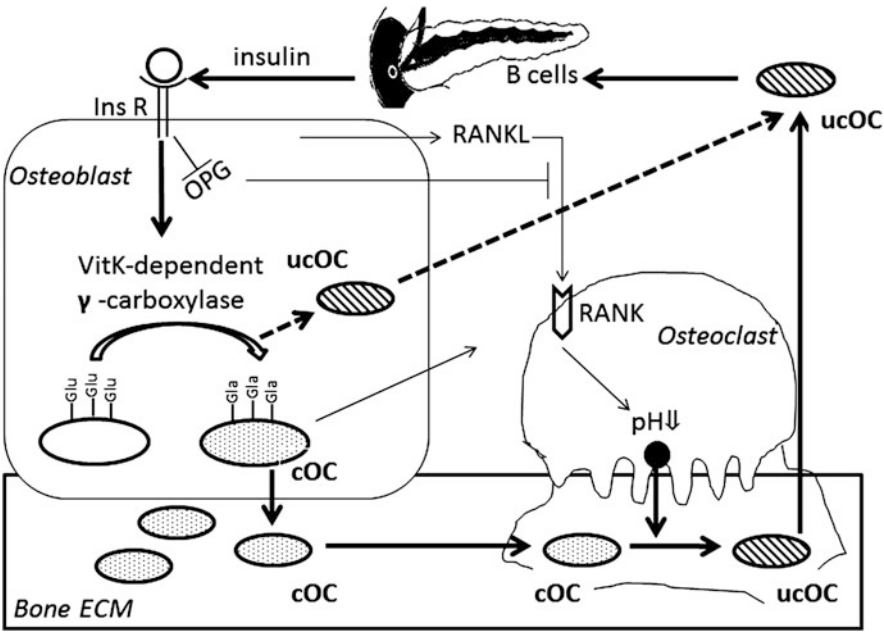

Fig. 8.5 A feedforward loop links insulin, bone resorption, and osteocalcin activity. Insulin signaling in osteoblasts acts on osteoblasts to facilitate osteocalcin synthesis via addition of a carbonate ion to a γ-glutamic acid residue by vitamin K-dependent **γ**-carboxylase, which is then secreted as γ-carboxylated osteocalcin (cOC). Secreted cOC is stored in the bone extracellular matrix (ECM). Furthermore, insulin signal inhibits the synthesis of osteoprotegerin (OPG). Because a decrease in OPG secretion enhances the function of osteoclast differentiation factor (RANKL), bone resorption by osteoclasts was activated. The acidic pH in resorption lacunae decarboxylates cOC stored in the bone EMC. Undercarboxylated osteocalcin (ucOC) then stimulates insulin secretion by the β-cells of the pancreatic islets. Ins R, insulin receptor

blood [23]. ucOC functions as an endocrine hormone for pancreatic β-cells and adipocytes. In pancreatic β-cells, ucOC facilitates insulin secretion, whereas it facilitates the secretion of adiponectin in adipocytes. For this reason, when ucOC is administered to mice, insulin sensitivity is increased, and blood glucose increases after glucose loading is suppressed [25]. Furthermore, ucOC administration causes a decrease in the amount of fat [25]. These results suggest that bone tissue creates a positive feedback mechanism that acts on pancreatic β-cells and adipose tissues via hormones such as ucOC and insulin, implying the presence of a close relationship between bone metabolism and glycometabolism.

8.2.3 Association of Osteocalcin with Diabetes

Clinical examinations have also been conducted to investigate the association of osteocalcin with glycometabolism and insulin sensitivity in humans. A cross-sectional study in patients with type 2 diabetes revealed that a decrease in ucOC was associated with fasting blood sugar levels and high HbA1c levels. In addition, its association with increases in body fat and the ratio of visceral fat to subcutaneous fat was revealed using a dual-energy X-ray absorptiometry method and CT, respectively [26]. In a large-scale cross-sectional study that involved 2,966 elderly males (70–89 years old), the levels of ucOC, total osteocalcin (TOC), and collagen type IC-terminal cross-linked telopeptide (CTX), which is a bone resorption marker, were all significantly reduced in patients with diabetes compared with those in nondiabetic patients, and these levels were associated with an increased risk of developing diabetes, independently of age, BMI, and renal function. In a multivariate model in which ucOC, TOC, and CTX were simultaneously incorporated, although both ucOC and CTX were risk factors for developing diabetes, TOC demonstrated no significant association, indicating that ucOC was involved in glycometabolism independently of bone metabolism turnover [27]. Even in hemodialysis patients with abnormalities of bone metabolism, increased levels of ucOC, which were associated with bone metabolism markers, were inversely associated with indices of glucose metabolism such as plasma glucose, hemoglobin A1c, and glycated albumin [28]. Concerning its association with insulin sensitivity, a longitudinal study in elderly males (55–80 years old) demonstrated that the rate of ucOC increase was related to the rate of HOMA-IR decrease [29], which is an index of insulin resistance. According to a study by Levinger et al., a significant increase in ucOC was observed together with increased insulin sensitivity after a 60-min exercise load, whereas no change was observed in TOC. In addition, an association was observed between the ucOC increase and the increase in insulin sensitivity before and after exercise [30]. These reports suggest that ucOC affects both insulin secretion and insulin sensitivity enhancement.

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