Chapter 6
Mechanism for the Development of Bone Disease in Diabetes: Renal Bone Disease

Yasuo Imanishi and Masaaki Inaba

Abstract Bone fragility is caused by chronic kidney disease (CKD). Renal osteodystrophy induced by secondary hyperparathyroidism of uremia is considered the main factor for the bone disease. Meanwhile, studies on degeneration of bone quality in CKD have recently advanced, and development of diagnostic and treatment methods is awaited.

Keywords Osteoporosis • Chronic kidney disease (CKD) • Chronic kidney disease-mineral and bone disease (CKD-MBD) • Bone quality

6.1 Introduction

Fragility fracture in osteoporosis may impair the patient's activities of daily living or lead to a bedridden state. As a result, not only is the patient's quality of life substantially lowered, but the patient's life prognosis may also be threatened. At the 2001 Consensus Meeting of the National Institutes of Health in the United States, osteoporosis was defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture [1]. Bone fragility is worsened, and the fracture risk is increased in osteoporosis due to reduced bone mass and lowered bone quality associated with bone microstructure.

In chronic kidney disease-mineral and bone disorder (CKD-MBD), serum calcium (Ca) and phosphate (P) concentrations are important factors in determining prognosis [2]. Regulation of Ca and P concentrations is related to bone fragility caused by secondary hyperparathyroidism of uremia (SHPT) [3] and to cardiovascular death [4].

Diagnosis and management of osteoporosis in patients with CKD stages 1–3 and patients without CKD are similar, but diagnosis and management decisions differ greatly once patients have CKD stages 4–5 [5]. Accordingly, the impaired bone quality as well as CKD-MBD, in addition to the lowered bone density, must be understood and controlled in order to deal with osteoporosis in CKD.

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6.2   Bone Fragility in Chronic Renal Disease

In addition to osteoporosis, fragility fracture-associated metabolic bone diseases include osteomalacia, osteogenesis imperfecta, fibrocystic osteitis, bone metastasis of malignant tumor, osteopetrosis, and Paget's disease of bone. Renal osteodystrophy (ROD) in CKD-MBD is important because of the large number of patients with ROD.

6.2.1   Renal Osteodystrophy

ROD is a collective term for different bone diseases observed in CKD-MBD. Not only osteoporosis but also fibrocystic osteitis, osteomalacia, aplastic bone disease (aluminum bone disease included), and amyloid bone disease are included in ROD-related diseases that induce bone fragility. Therefore, in cases of advanced CKD, a bone biopsy is sometimes required to confirm the histological type [6]. Bone morphometry-based bone turnover, mineralization, and volume (TMV) classification (Table 6.1) has recently been used for histological classification of ROD and is an important assessment method for ROD [6].

6.2.2   Bone Mineral Density in CKD

According to a survey of 2174 Japanese men age 65 or older, bone density of lumbar spine and femur was negatively correlated to renal function [7]. Furthermore, a meta-analysis of the patients with end-stage renal failure (CKD stage 5) showed that bone density was low in the patients who had previously experienced bone fractures [8], suggesting that bone density measurement may be useful for fracture risk assessment in CKD stage 5. However, the prevalence of fracture in the proximal femur is higher in patients on maintenance hemodialysis (CKD stage 5D), regardless of age or sex, compared with the general public [9], indicating that CKD itself is a factor for bone fragility.

Table 6.1 TMV classification system for renal osteodystrophy [6]

Turnover	Mineralization	Volume
High	Normal	High
Normal	Abnormal	Normal
Low		Low

TMV bone turnover, mineralization, and volume

6.2.3   Residual Renal Function and Bone Fragility

Even in CKD stages 1–3 with mild renal dysfunction, lower renal function has been shown to be a risk for fracture in the proximal femur, after correction for bone density [10]. Accordingly, bone density alone has a limitation in assessing bone fragility in CKD as in the case of diabetes [11].

Fracture prevalence is particularly high in CKD patients with a glomerular filtration rate (GFR) <60 mL/min, and their prevalence has been reported as 2.12 times that of the patients with GFR ≥60 mL/min [12]. Furthermore, as already mentioned (Sect. 6.2.2), maintenance hemodialysis patients with advanced renal dysfunction (CKD stage 5D) have a higher prevalence of proximal femur fracture than the general population, regardless of age or sex [9]. Even in the CKD stage 5D patients on hemodialysis for less than 1 year, their prevalence of proximal femur fracture is higher compared with non-CKD patients, a trend that continues over a long time [13] (Fig. 6.1).

6.2.4   SHPT and Bone Fragility

In CKD stage 5D patients, the prevalence of SHPT associated with a marked increase of parathyroid hormone (PTH) is still high, which is a risk factor for
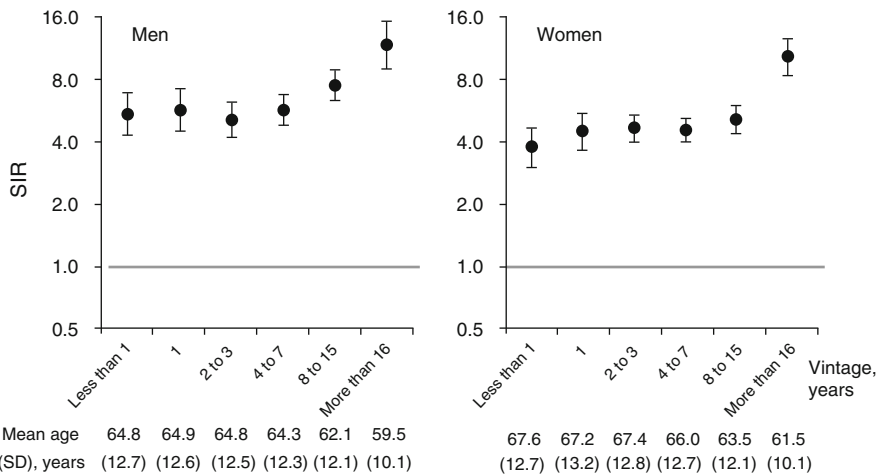

Fig. 6.1 Incidence of proximal femur fracture after introduction of hemodialysis [13]. Standardized incidence ratios (SIRs) stratified by vintage for men and women and standardized for age. *Error bars* indicate 95 % confidence intervals. Less than 1 year after introduction of hemodialysis, SIR was already substantially higher than that of the general public (*horizontal line* set as 1.0 on the y-axis), a trend that continued for 15 years after hemodialysis introduction. At 16 years and beyond, SIRs rapidly increased

fracture. An excessive increase of PTH in SHPT worsens ROD, particularly osteitis fibrosa, increasing the fracture risk [3].

Increased bone turnover in SHPT is considered a factor for bone fragility in CKD [14]. According to a report on cross-sectional examination of bone biopsy specimens of CKD stage 5D patients, bone turnover markers, namely, osteon activation frequency and bone formation rate, are negatively correlated with serum sclerostin and positively correlated with serum intact PTH [15], and this finding is one piece of the evidence for PTH's acceleration of bone turnover.

6.2.5 Bone Quality in CKD

In CKD, only a weak correlation is found between bone density and fracture rate, compared with primary osteoporosis [16]. Therefore, decreased bone quality, rather than decreased bone density, is suspected as a factor for fragility fracture in CKD. Bone quality deteriorates due to advancement of hyperhomocysteinemia in association with progression of CKD [17], thereby increasing formation of pentosidine cross-links, which are nonphysiological cross-links for type 1 collagen in bone tissue, and bone fragility develops [18]. According to a study on iliac biopsies of CKD stage 5D patients with advanced SHPT, mature cross-links decreased and immature cross-links increased in bone tissue [19]. The content of pentosidine increased substantially in the bone tissue of CKD stage 5D patients compared with that of healthy people, and bone formation rate per bone volume and mineral apposition (bone calcification) rate were inversely proportional. Based on the above, the increase in advanced glycation end-product cross-links such as pentosidine cross-links is strongly related to abnormal bone metabolism in CKD stage 5D patients.

Bone density cannot accurately assess fracture risk because of technological problems with bone densitometry measured by dual-energy X-ray absorptiometry (DXA). High-resolution peripheral quantitative computed tomography (HR-pQCT) for peripheral bones produces images of minute bone tissues and therefore is more reliable than DXA for evaluation of osteoporosis [20]. HR-pQCT is particularly good for evaluating cortical bone. In CKD patients, cortical bone becomes osteoporotic due to SHPT and acceleration of bone metabolic turnover [21]. Because osteoporosis of cortical bone cannot be captured by a traditional DXA, it is considered an aspect of bone quality.

6.2.6 Other Factors Affecting Bone Fragility in CKD

In a retrospective cohort study of 144 patients with CKD stage 5D using the onset of fragility fracture as the outcome [22], sex (female), fracture history, decreased radial bone density, relative hypoparathyroidism, and vitamin D deficiency were

Table 6.2 Correlates of bone fracture in prevalent hemodialysis patients

	OR	P	95 % CI
Sex (female)	18.092	0.026	1.406–232.937
Fracture before HD	73.786	0.001	6.143–886.217
Previous transplantation	0.462	0.541	0.039–5.508
Duration of RRT	0.998	0.740	0.986–1.010
iPTH <100 pg/mL	37.774	0.022	1.694–842.189
iPTH >300 pg/mL	1.981	0.499	0.273–14.372
Kt/V	0.023	0.154	0.000–4.141
Radius Z-score (1-SD decrease)	2.691	0.006	1.327–5.459
25-OHD <20 nmol/L	11.215	0.026	1.326–94.813

In a multivariate logistic regression model, Hosmer-Lemeshow $\chi^2\ P = 0.811$ [22]
OR odds ratio, *CI* confidence interval, *HD* hemodialysis, *RRT* renal replacement therapy, *iPTH* intact parathyroid hormone, *Kt/V* efficiency of hemodialysis, *SD* standard deviation, *25-OHD* 25-hydroxyvitamin D

found to be independent risk factors for fragility fracture (Table 6.2). Even in healthy people without reduced kidney function, the level of vitamin D sufficiency and prevalence of proximal femur fracture are correlated [23]. In patients on CKD stage 5D, attention should be paid not only to the decrease of serum 1,25-dihydroxyvitamin D (1,25-$(OH)_2$D) but also to the level of nutritional vitamin D sufficiency or serum 25-hydroxyvitamin D (25-OHD) level.

In the present study, relative hypoparathyroidism was demonstrated as a significant risk factor for fragility fracture [22] (Table 6.2). Excessive suppression of bone metabolism may delay the repair of bone microdamage, leading to the onset of fragility fracture.

6.3   Chronic Kidney Disease-Mineral and Bone Disease

With progression of CKD, calcium and phosphate homeostasis collapses and risk of death and cardiovascular events increases [2]. In CKD, bone diseases and ectopic calcification develop concurrently. Therefore, the term "chronic kidney disease-mineral and bone disorder (CKD-MBD)" has been recommended to represent the concept of bone mineral metabolism disorder [6].

6.3.1   Calcium and Phosphate Homeostasis

Homeostasis for calcium (Ca) and phosphate (P) concentrations in serum involves three hormones: PTH, 1,25-$(OH)_2$D, and fibroblast growth factor 23 (FGF-23). PTH, 1,25-$(OH)_2$D, and FGF-23 form a feedback loop with Ca and P [24] (Fig. 6.2).
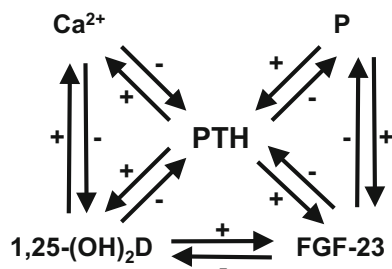
Fig. 6.2 Feedback loops in calcium and phosphate homeostasis [24]. Calcium and phosphate homeostasis is regulated by three hormones: parathyroid hormone (PTH), 1,25-dihydroxyvitamin D (1,25-$(OH)_2$D), and fibroblast growth factor 23 (FGF-23). A feedback loop is formed between respective factors, playing an important role in serum Ca-P homeostasis

Table 6.3 Receptors in parathyroid cells affecting PTH secretion [25]

Receptor	Location
VDR	Cell nucleus
CaSR	Cell membrane
FGFR-Klotho complex	Cell membrane

VDR vitamin D receptor
CaSR calcium-sensing receptor
FGFR fibroblast growth factor receptor

Furthermore, PTH, 1,25-$(OH)_2$D, and FGF-23 form feedback loops among each other. These hormones play an important role in serum Ca-P homeostasis.

PTH, produced from the parathyroid gland, is important for the minute-to-minute regulation of serum Ca concentration. In the parathyroid gland, there are vitamin D receptors (VDRs), calcium-sensing receptors (CaSRs), and fibroblast growth factor receptor (FGFR)-Klotho complexes [25] (Table 6.3), which transmit to parathyroid cells information regarding the 1,25-$(OH)_2$D, Ca, and FGF-23 concentrations in the blood, respectively, thus modulating PTH secretion.

CaSR, in particular, has an important role in regulating serum Ca concentration. CaSR is a seven-transmembrane receptor in the parathyroid cell membrane. PTH is a hormone with high responsiveness for maintaining the serum Ca concentration. The parathyroid cell is highly sensitive to the changes in extracellular Ca concentration and regulates PTH secretion accordingly [25] (Fig. 6.3). Cinacalcet and other CaSR agonists modulate CaSR allosterically and make the parathyroid cell behave in a way as if the extracellular Ca concentration were high. In addition to the regulation of PTH release from the secretory granules in the parathyroid cell [26], cinacalcet is involved in PTH gene transcription and posttranscriptional regulation [27]. Furthermore, cinacalcet is involved in the regulation of parathyroid cell growth [28] and also contributes to the PTH secretion regulatory mechanism.

FGF-23 is produced from bone and can regulate serum phosphate concentration without causing much change in the serum Ca concentration. Secretion of FGF-23 from osteocytes is regulated by dietary phosphorus loading, 1,25-$(OH)_2$D, and PTH [24] (Fig. 6.2). The FGFR-Klotho complex is a receptor for FGF-23. In Klotho-mutant mice, the function of Klotho (part of the receptor) is deficient, and
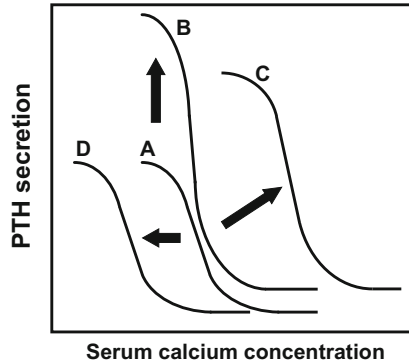
Fig. 6.3 Extracellular calcium-induced changes in the parathyroid hormone (PTH) secretion-regulating mechanism and changes in pathological condition [25]. (**a**) Normal PTH-Ca sigmoid curve. In accordance with the changes in serum calcium, PTH is produced. The serum calcium concentration corresponding to the midpoint PTH value between maximal and minimal PTH secretion is called the set point, which is used to evaluate parathyroid sensitivity to serum calcium concentration. The increase of the set point indicates a reduction of sensitivity to serum calcium, suggesting decreased calcium-sensing receptor (CaSR) expression in the parathyroid. (**b**) The case where only the number of secretory cells increases with no set-point abnormality. The PTH-Ca sigmoid curve only moves upward with no rightward shift and no hypercalcemia. (**c**) In primary hyperparathyroidism or severe secondary hyperparathyroidism, the number of secretory cells increases, and the PTH-Ca sigmoid curve moves upward, thus reducing CaSR expression in the parathyroid, with elevation of the set point and a rightward shift of the PTH-Ca sigmoid curve. In such a condition, hypercalcemia and excessive PTH concentration in the blood may coexist. (**d**) In autosomal dominant hypocalcemia induced by an activating mutation of the CaSR, parathyroid sensitivity to serum Ca increases, with a leftward shift of the PTH-Ca sigmoid curve due to the lowered set point. Calcimimetic CaSR agonists such as cinacalcet also lower the set point

acceleration of aging and ectopic calcification have been reported [29]. The phosphorus metabolism regulatory system controlled by the FGF-23 signaling has an important role in Ca-P homeostasis in the blood, particularly in suppression of ectopic calcification.

6.3.2 Pathogenesis of SHPT

In the initial stage of CKD, the serum Klotho concentration decreases first and then the serum FGF-23 concentration increases [30] (Fig. 6.4). With progression of CKD, the elevation of serum phosphorus concentration cannot be suppressed by only the increased FGF-23, leading to an increase of PTH. When FGF-23 and PTH finally fail to regulate phosphorus metabolism, the serum phosphorus concentration rises.

Acceleration of PTH synthesis/secretion, parathyroid cell growth, and parathyroid hyperplasia occur due to hyperphosphatemia-induced relative hypocalcemia, a
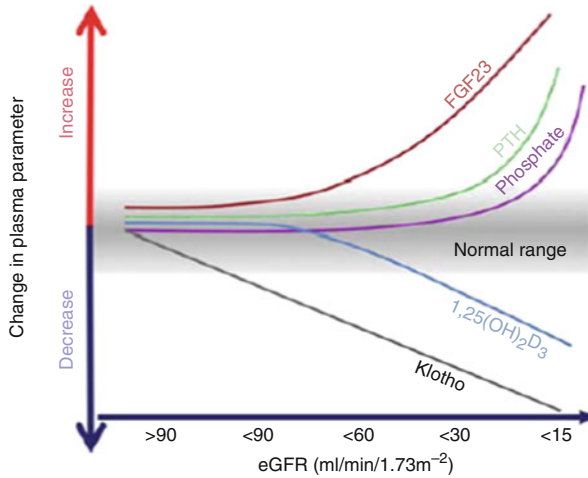
Fig. 6.4 Time profile of changes in plasma fibroblast growth factor 23 (FGF-23), Klotho, active vitamin D, and phosphate levels as chronic kidney disease (CKD) progresses [30]. With progression of CKD, the serum Klotho concentration decreases and the serum FGF-23 concentration increases, thereby suppressing the elevation of serum P concentration. However, with further deterioration of renal function, the 1,25-dihydroxyvitamin D_3 (1,25-$(OH)_2D_3$) concentration decreases, and the serum parathyroid hormone (PTH) concentration increases in order to maintain the serum P concentration, but the serum P concentration goes up due to substantial progression of CKD. *eGFR* estimated glomerular filtration rate

direct effect of hyperphosphatemia on the parathyroid, and vitamin D activation disorder. In such conditions, PTH activity becomes excessive, transferring phosphorus from bone to blood and further aggravating the hyperphosphatemia, leading to progression of CKD. Even if hemodialysis or peritoneal dialysis is introduced, its capacity to remove phosphorus is limited, and hyperphosphatemia persists, resulting in aggravation of SHPT.

According to the analysis of uremia-associated parathyroid tumors removed by parathyroidectomy (PTX) in the patients with medically refractory SHPT, many of these tumors were found to be monoclonal tumors (produced from a single cell) with somatic mutations [31]. The parathyroid initially demonstrates diffuse hyperplasia due to polyclonal growth but undergoes somatic mutation by a persistent proliferative stimulus and finally progresses to monoclonal nodular hyperplasia originating in a single cell [24] (Fig. 6.5). In such uremia-associated parathyroid tumors, decreased expression of VDR and CaSR is observed [32, 33].

Reduction of CaSR expression in the cellular membrane induces an abnormality in the extracellular Ca-sensing mechanism. The mechanism of regulating PTH secretion according to the serum Ca concentration is then impaired, and the PTH-Ca sigmoid curve is shifted to the right [24] (Fig. 6.3), indicating that a higher concentration of extracellular Ca is required to suppress PTH secretion. When the sigmoid curve is shifted substantially to the right due to progression of SHPT, the
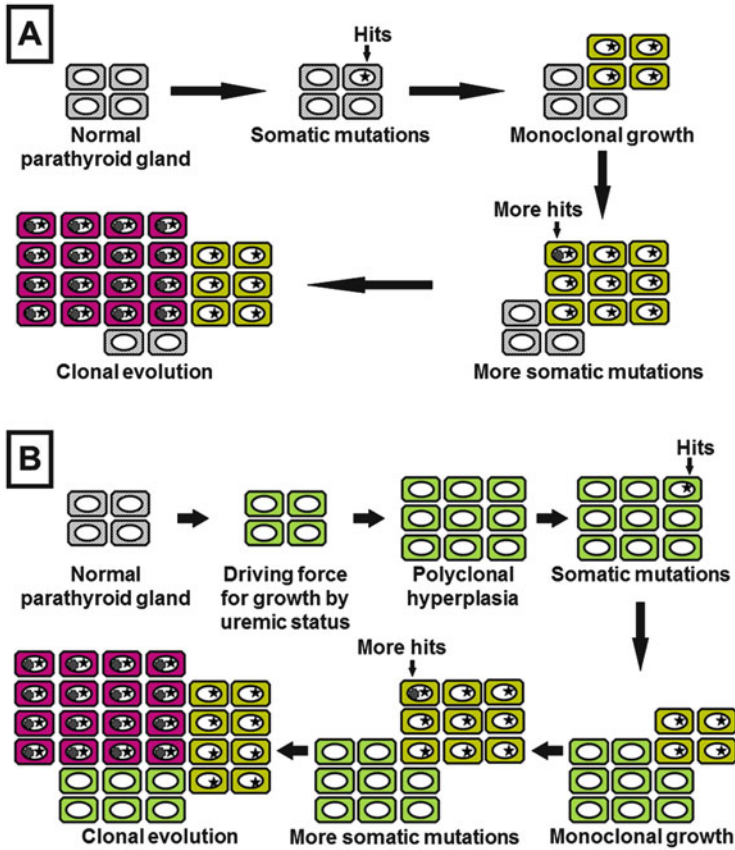
Fig. 6.5 Formation of uremia-associated parathyroid tumors (modification of reference [24]). (**a**) In primary hyperparathyroidism (parathyroid adenoma), a sequence of somatic mutations occurs and provides the cells with proliferative predominance. In such cells with increased proliferative potency, additional somatic mutations are likely to occur. Eventually, monoclonal tumors are formed. (**b**) With progression of chronic kidney disease (CKD), polyclonal parathyroid tumors are formed by growth stimulation on parathyroid gland. The actively dividing cells are likely to induce somatic mutations. As a result of proliferative predominance through somatic mutation, monoclonal uremia-associated parathyroid tumors are formed

serum Ca concentration may sometimes exceed the normal level to induce hypercalcemia.

Due to progression of CKD and hyperphosphatemia, the activity of 1-α-hydroxylase in kidney tubules decreases, and the serum 1,25-$(OH)_2$D concentration is reduced. In the parathyroid, expression of VDR, one of the nuclear receptors, is reduced [32]. The PTH secretion-suppressing activity via 1,25-$(OH)_2$D and parathyroid cell proliferation-suppressing activity are disturbed, resulting in further progression of SHPT.

In the physiological state, FGF-23 has phosphaturic activity as well as PTH secretion-suppressing activity. In the patients on maintenance hemodialysis (CKD5D), despite a substantial increase of the FGF-23 concentration in blood, FGF-23 is positively correlated with PTH. Even a high concentration of FGF-23 cannot sufficiently suppress PTH secretion [34], possibly because reduction of Klotho and FGFR expression in the parathyroid gland [35] impairs the FGF-23 signal transmission to parathyroid cells via the FGFR-Klotho complex, leading to the failure to suppress PTH secretion.

As discussed above, PTH secretion and parathyroid cell proliferation increase due to hyperphosphatemia, impaired vitamin D activation, and dysfunctions of various receptors in the parathyroid gland (CaSR, VDR, and FGFR-Klotho complex) (Table 6.3), finally resulting in the substantial collapse of Ca-P homeostasis in serum [25].

6.3.3   Role of FGF-23 in Bone Fragility

In Swedish-elderly males who participated in the multicenter prospective MrOS study, a positive correlation was demonstrated between serum FGF-23 concentration and fracture [36]. After correction for renal function, correlations were found between FGF-23 concentration and the total fracture risk (age-corrected hazard ratio 1.20 [95 % confidence interval 1.03–1.40]) and vertebral facture risk (age-corrected hazard ratio 1.33 [95 % confidence interval 1.02–1.75]). In this study, whether FGF-23 itself induced bone fragility could not be determined, but FGF-23 was shown to be a prognostic factor for fracture risks.

When phosphaturia is likely to occur without much impairment of renal function, excessive FGF-23 may cause bone calcification disorder due to hypophosphatemia and vitamin D activation disorder induced by accelerated phosphaturia [37]. However, in CKD, there is no or a very limited incidence of phosphaturia, and the state of hypophosphatemia does not emerge, which raises the question of whether or not the bone tissue would be directly affected by excessive FGF-23 levels in the blood of CKD patients.

In a cellular experimental system (in vitro), excessive FGF-23 has been reported to suppress osteoblast differentiation and matrix calcification, via FGFR1 [38], indicating a direct effect of FGF-23 on bone tissue. However, in a model mouse of primary hyperparathyroidism with accelerated bone turnover, FGF-23 gene expression increased in bone tissue [39]. Increased FGF-23 in fracture patients may be caused by accelerated bone turnover. The question of a direct effect, or not, of FGF-23 on bone will have to be further studied.

6.4 Treatment for Bone Fragility in CKD

ROD classification-based treatment is recommended for the patients with advanced CKD, when lower bone density or bone fragility is observed, and a bone biopsy is sometimes required to confirm the histological type [6]. However, a bone biopsy is not always carried out before treatment, and treatment may be started by guesswork regarding histological type based on metabolism markers and other serological test results. Treatment of bone in CKD is usually carried out with three types of agents: antiresorptive agents such as bisphosphonate, denosumab, and selective estrogen receptor modulators (SERMs); osteoporosis drugs such as bone-forming agents (e.g., teriparatide); and drugs used to treat CKD-MBD.

6.4.1 Bisphosphonates

In nine clinical studies including 8,996 women with CKD (stages 1–3) and post-menopausal osteoporosis, risedronate was found to reduce the fracture rate [40], even in a group with significant renal dysfunction (median GFR ≤30 mL/min). In the Fracture Intervention Trial (FIT), alendronate lowered the fracture rate, regardless of renal function at the start of the trial [8]. However, in a 6-month placebo-controlled study in CKD5D patients, alendronate significantly, although modestly, suppressed the decrease of femoral bone density [41]. Therefore, the usefulness of bisphosphonates in CKD5D will have to be further examined. Although the use of bisphosphonates in CKD is an interesting subject, awareness is needed in advanced CKD that it may result in adynamic bone formation.

6.4.2 Denosumab

In mild to moderate CKD, the efficacy of denosumab has been demonstrated [42]. However, hypocalcemia has been reported to develop in some patients with kidney failure requiring hemodialysis [43]. Therefore, denosumab must be cautiously administered in advanced CKD patients.

6.4.3 Selective Estrogen Receptor Modulators

Aiming to elucidate the fracture-preventing activity of raloxifene, a large-scale clinical study (Multiple Outcomes of Raloxifene Evaluation [MORE] study) was carried out in 180 centers of 25 countries. The subjects were 7705 osteoporotic women at least 2 years away from menopause. Whether or not they had fractures
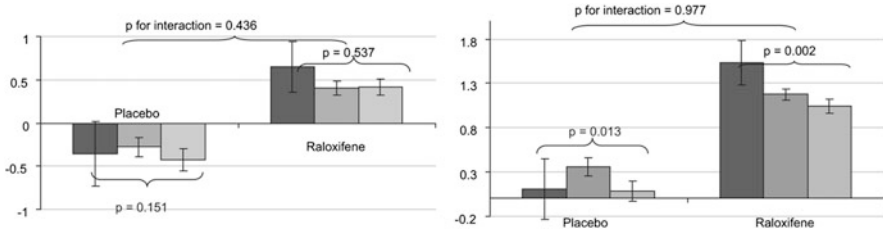
Fig. 6.6 Effect of raloxifene to increase bone density [45]. From among 7,705 participants in the MORE study, 7,316 patients (chronic kidney disease stages 1–3) whose serum creatinine had been determined at the time of study initiation were reanalyzed. Analysis was made of three groups divided by estimated glomerular filtration rate calculated by the modification of diet in renal disease (MDRD) method: $\leq$45, 45–59, and $\geq$60 mL/min. In all of the groups, raloxifene increased lumbar and vertebral density and reduced the rate of vertebral compression fracture. No effects were found on the nonvertebral fracture rate

previously, the onset of new vertebral fracture was prevented [44]. From among the MORE study participants, 7316 patients whose serum creatinine had been measured at the time of study initiation were reanalyzed. Regardless of the level of renal function, raloxifene increased femoral bone density and vertebral bone density. It further reduced the vertebral compression fracture rate [45] (Fig. 6.6). Bazedoxifene, an SERM, lowered bone metabolism marker levels, regardless of renal function before treatment, and improved lumbar and femoral density [46]. Furthermore, no serious adverse reactions were reported in association with renal dysfunction.

In a study of CKD5D, raloxifene increased vertebral density [47]. Furthermore, administration of raloxifene for 1 year improved calcaneal density and bone metabolism marker levels in diabetic as well as nondiabetic CKD5D patients [48]. Based on these findings, SERMs are considered useful in improving bone fragility of CKD patients including CKD5D patients.

6.4.4 Teriparatide

Although the efficacy of teriparatide was demonstrated in mild to moderate CKD [49], it is considered a contraindication for patients with SHPT [50]. Some people recommend teriparatide for CKD with adynamic bone disease [51]. However, a report suggested that the bone of CKD patients is less responsive to PTH [52], and therefore, further investigation is required in this area.

6.4.5   Therapy for CKD-MBD

Dietary therapy is first conducted to sufficiently control the serum P level. However, in the case of insufficient control, a phosphate binder should be orally administered. In the past, calcium-based phosphate binders (e.g., calcium carbonate) were used, but the concurrent use of VDR agonists (VDRAs) easily induced hypercalcemia or increased the calcium-phosphate product, and therefore, non-calcium-based phosphate binders such as sevelamer hydrochloride and lanthanum carbonate have been more frequently used.

In the parathyroid gland, VDRAs suppress PTH gene transcription and PTH secretion as well as proliferation of parathyroid cells. However, in the uremia-associated parathyroid tumors, the expression of VDR, the target molecule for VDRAs, is reduced, and therefore, the effect of the VDRA is limited. Furthermore, VDRAs accelerate calcium absorption in the small intestine, inducing hypercalcemia depending upon the dose level. Accordingly, the dosage level is restricted, and serum PTH cannot be fully suppressed in many cases.

CaSR agonists (calcimimetics) allosterically act on the CaSR in the parathyroid gland and suppress PTH secretion [26, 53], thus reducing the serum calcium-phosphate product. Furthermore, the calcimimetics inhibit parathyroid cell proliferation [28]. The effect of calcimimetics is maintained to a certain level even in parathyroid tumors where expression of the target CaSR is reduced [54].

According to the results of a combined analysis of four studies on cinacalcet in maintenance hemodialysis patients, the risks for PTX-, fracture-, and cardiovascular event-related hospitalization were significantly reduced by cinacalcet [55]. Furthermore, in maintenance hemodialysis patients in the EVOLVE trial, cinacalcet significantly reduced the incidence of fracture with a hazard ratio of 0.84 by intention-to-treat analysis after correction for fracture risk factors (history of fracture, age, smoking, etc.) [56].

PTX is recommended for SHPT that is refractory to medical treatment. In a matched cohort study to monitor the long-term effect of PTX, PTX reduced the occurrence of femoral fracture by 32 % and the combined rate of fracture in femur, vertebra, and distal forearm by 31 % [57]. However, sometimes there are five or more parathyroid glands, and ectopic parathyroid tumors may be found in the mediastinum or thyroid. Therefore, the parathyroid should be fully observed before and during surgery. Subtotal resection, total resection, and autograft after total resection are recommended as surgical procedures.

6.5 Conclusion

CKD stages 1–3 patients can be treated by the same drug therapy as osteoporotic patients with normal renal function. However, the treatment of CKD-MBD is the central therapy for CKD stages 4, 5, and 5D. SHPT control, in particular, can reduce cardiovascular events and prevent fragility fracture in CKD-MBD.

In CKD patients, decreased bone quality due to deterioration of the collagen bridge is another cause of bone fragility. Improvement of bone quality by SERM treatment is expected to reduce the fracture rate. Progression of osteoporosis in cortical bone is also considered to reduce bone quality in CKD. However, it is still difficult to evaluate bone quality in the clinical setting. Further advancement in this area is expected for the future.

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