Bone Health in Chronic Kidney Disease

30

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Introduction

Osteoporosis is the most prevalent condition leading to low-trauma fractures in humans worldwide. Many metabolic disturbances, including renal bone disorders, lead to osteoporosis and the pathologic fractures associated with osteoporosis and non-osteoporotic fragility fractures. Osteoporosis can be part of the impaired bone quality (altered architecture, remodeling, mass, and volume) seen in chronic kidney disease-mineral bone disease (CKD-MBD) patients; however, despite this overlap, osteoporosis and CKD-MBD progress via distinct pathways, each resulting in impaired bone strength and higher risk of low-trauma fracture.

The prevalence of osteoporosis varies according to chronic kidney disease (CKD) stage. Early CKD patients, from stages 1 to 3, do not exhibit altered bone strength or pathological fractures according to any prospective or observational data, even with the presence of mildly elevated PTH level and intermittent hyperphosphatemia. Thus, any fracture in these early CKD stages is mostly associated with osteoporosis, rather than CKD-MBD. Derangements in phosphorus, PTH, or bone turnover markers or bone histomorphometry associated with CKD-MBD can be seen as early at stage 3 CKD. Most patients with stage 4 and 5 CKD exhibit alternations in bone quality due to metabolic bone disorders and/or decreases in BMD [1, 2]; at the time of initiation of dialysis, up to 50% of patients have had a fracture [3, 4]. Furthermore, CKD patients are more commonly associated with poor nutrition, inactivity, myopathy, and peripheral neuropathy, which altogether play a role in muscle weakness and falls [5]. A study conducted by Huang et al. revealed that advanced age, low body weight, low serum albumin level, and high ALP and iPTH levels were

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associated with low bone mass in hemodialysis patients [6].

CKD is associated with higher morbidity and mortality fractures. The third National Health and Nutrition Examination Survey of 6270 men and women showed a twofold increased risk of hip fracture in those with an estimated glomerular filtration rate (eGFR) < 60 mL/min, as compared to those with an eGFR ≥60 mL/min [7]. The Study of Osteoporotic Fractures surveyed 9704 women of 65 years and older and revealed a 1.5-fold increased hip fracture risk among those with an eGFR between 45 and 50 mL/min and a twofold increase among women with an eGFR <45 mL/min, when compared to women with an eGFR ≥60 mL/min [8]. Another cross-sectional study conducted on 5481 elderly men and women also revealed that those with an eGFR <65 mL/min had an approximate 1.5-fold increased risk of hip, spine, and wrist fractures, compared to those with eGFR >65 mL/min [9]. The incidence of fractures increases with advanced CKD stage and is highest in stage 5 CKD patients on dialysis. A large retrospective study based on data from the United States Renal Data System (USRDS) showed an increased relative risk of hip fracture in both men and women with stage 5 CKD on dialysis, compared to the general population [10]. After suffering a hip fracture, these stage 5 CKD patients on dialysis also had an increased 1-year mortality rate of 64%, as compared to the 15–20% 1-year mortality rate in the general population; this patient group also tended to experience hip fracture at a younger age compared with the general population (16 and 13 years earlier among men and women, respectively) [11]. Knowing which patients are at a higher risk for fractures and falls among CKD patients may enable the establishment of protocols to decrease the economic costs, morbidity, and mortality associated with fractures in this patient group. In CKD patients with severe pathological fractures, assessment of bone markers and, in some cases, bone biopsy may be needed to diagnose CKD-MBD with osteoporosis, which may influence the prescribed pharmacological therapies.

Mechanisms Underlying the Development of Osteoporosis

Dysregulation of RANK/RANKL/OPG System (Fig. 30.1)

Bone tissue is composed of osteocytes, osteoblasts, and osteoclasts, which interact with each other. The quality of bone and mass of bone tissue are determined by bone remodeling [13]. Bone remodeling is characterized by coordination between anabolic and catabolic phases. Regulators such as parathyroid hormone (PTH) and calcitriol and hormones such as growth hormone, glucocorticoids, thyroid hormones, estrogen, insulin-like growth factors, prostaglandins, tumor growth factor-βa, bone morphogenetic proteins (BMPs), and cytokines affect the balance between the anabolic and catabolic phases of bone remodeling [14]. Molecular-level bone remodeling is regulated by the receptor activator of the NF-κB (RANK)/RANKL/osteoprotegerin (OPG) system. RANK present on the surface of osteoclasts induces osteoclast activation and proliferation upon binding to RANKL that is produced by osteoblasts [15, 16] and promotes bone resorption. OPG, which is secreted by osteoblasts, functions as a decoy receptor for RANKL, prevents RANKL from binding to RANK [15], and prevents excessive bone resorption. At the initial phase of bone resorption, osteoclast activation inhibits osteoblast formation by inducing a Sema4D/plexin/B1 signal, which transiently

1. Dysregulation of RANK/RANKL/OPG system
- Excessive osteoclast activity (OCs≠; more bonr resorption)
- Eg.: High PTH, Estrogen Deprivation, RA, SLE

2. Excessive Wnt signaling inhibitors
- Insufficient osteoblast function (OBs ; less bone formation)
- Eg.: CKD, Menopause, Vasxular calcification

3. Inflammatory cytokines related osteolysis
- Excessive Osteoclast activity (OCs≠; more bone resorption)
- Eg.: Intestinal microbiota, Vit-D deficiency

Fig. 30.1 Mechanism related to major causes of osteoporosis [12]

inhibits bone formation during bone resorption [17]. At the end of bone resorption, after the removal of apoptotic osteoclasts by macrophages, osteoblast precursor cells are recruited from the bone marrow to the bone matrix where they undergo differentiation into osteoblasts and osteocytes [18]. Thus, the RANKL/OPG system tightly couples bone resorption and formation to maintain skeletal integrity. The increased in RANK/RANKL and decreased in OPG levels will accentuate the osteoclast related bone resorption.

Excessive Wnt/β-Catenin Signaling Inhibitors

The Wnt signaling pathway in bone cells affects the osteoblast differentiation and bone formation [1]. Rare diseases that affect bone formation, such as van Buchem disease or osteoporosis-pseudoglioma syndrome, highlight the importance of the Wnt pathway in bone formation [1]. The Wnt signaling pathway has three major branches, namely, the canonical Wnt pathway [10], noncanonical Wnt–planar cell polarity pathway, and Wnt–calcium pathway. In the canonical Wnt pathway, binding of Wnt ligands to a dual receptor complex comprising frizzled (FZD) and LRP5 or LRP6 activates cytoplasmic β-catenin and decreases gene transcription [2]. Activation of the Wnt/β-catenin pathway represses the differentiation of mesenchymal stem cells into adipocytes and chondrocytes and promotes their differentiation into osteoblasts and osteocytes [3, 4]. Activation of the Wnt/β-catenin pathway in bone cells induces osteoblastogenesis and inhibits osteoclastogenesis. Wnt antagonists such as sclerostin and Dickkopf-related protein 1 (DKK1) offset osteoblastogenesis and inhibit bone formation [5, 6]. Other hormonal change such as increase in serum PTH enhanced the bone formation by inhibiting Wnt inhibitors [7] or by phosphorylating β-catenin [8]. Immobile stat decrese bone formation by increasing sclerostin, a Wnt signaling antagonist on osteoblasts produced by osteocytes [9]. Increased renal production and circulating levels of DKK1 in CKD have been associated with decreased osteoblastogenesis and increased osteoclastogenesis [10]. In addition, immunohistochemical staining of sclerostin indicating expression of the protein by osteocytes, vascular atherosclerotic lesions and calciphylaxis skin in CKD [11]. Thus, in CKD patients, excessive of Wnt/β-catenin signaling inhibitors (Dickkopf-related protein 1, DKK1 and Sclerostin, SOST) will attenuate the osteoblast viability and increase osteoclast activity resulted in an obvious bone loss.

Inflammatory Cytokine-Related Osteolysis

Inflammatory cytokines affect bone turnover. A study on patients with inflammatory arthritis indicated that excessive cytokine production induced osteoclast activation and bone resorption [19]. Cytokines released by type 1 T helper cells, such as tumor necrosis factor (TNF), interleukin-1 (IL-1), IL-17, and IL-23, activate osteoclastogenesis [20, 21]. IL-6 and soluble IL-6 receptor are suggested to act synergestically on osteoblasts to activate the differentiation of osteoclast precursor cells into osteoclasts [22]. TNF-α activates osteoclastogenesis beyond the RANKL/OPG signal [23]. These findings indicate that a cytokine or cytokine storm activates osteoclastogenesis, which may contribute to bone loss in the various clinical inflammatory scenarios.

Specific disorders that disturb bone homeostasis, such as overactivation of osteoclastogenesis or inhibition of osteoblastogenesis, decrease bone mass and promote osteoporosis.

Disturbed Bone Remodeling: High or Low Bone Turnover-Related Osteoporosis

Normal bone turnover is defined as an appropriate bone surface/volume, and the rate of bone remodeling is affected by the balance between bone formation and resorption [24, 25]. Higher bone turnover indicates higher bone resorption because of overactivation of osteoclastogenesis [26]. Increased osteoid formation and endplate

fibrosis are histopathological hallmarks of high bone turnover disorder. In patients with high bone turnover disorder, several metabolic diseases such as secondary hyperparathyroidism, systemic lupus erythematous, or other autoimmune disease; pregnancy; and postmenopausal disorder increase the activity of osteoclasts and accelerate bone resorption. By contrast, inhibited bone formation or accelerated osteoblast apoptosis decreases osteoclastogenesis and bone turnover. Nonanastamosing trabeculae and low osteoid layer are histopathological hallmarks of low bone turnover disorder [25]. In patients with low bone turnover disorder such as adynamic bone disorder, osteomalacia [27, 28], liver cirrhosis [29], and glucocorticoid-induced osteoporosis (GIO), osteoblast-induced bone formation is attenuated. Both high and low bone turnover disorders induce osteoporosis.

High Bone Turnover Disorder

High bone turnover disorder is induced by bone resorption due to osteoclast activation that exceeds osteoblast formation. Factors that stimulate osteoclast activity or alleviate calcification inhibitors induce bone resorption and decrease bone mass. Several diseases—such as secondary hyperparathyroidism, postmenopausal disorder, and systemic inflammation—accelerate bone turnover.

Secondary Hyperparathyroidism

Secondary hyperparathyroidism is common in patients with CKD, which is caused by phosphate retention induced by decreased renal excretion [30]. Progressive GFR lowering and nephron loss, a decrease in renal phosphate excretion, fibroblast growth factor 23 (FGF23) activation, and vitamin D deficiency increase parathyroid gland activation [31]. High PTH levels affect *RANKL* and *OPG* mRNA expression in osteoblasts and sequentially activate osteoclast-related bone resorption by activating the RANKL pathway [32]. PTH also regulates the hematopoietic niche by acting on osteoblasts by interacting with the Wnt pathway [33]. During the early stage of CKD, bone turnover is suppressed because of an increase in the expression of sclerostin and PTH receptor-1 in bone. Excessive osteoblastic activity compensates for bone resorption, resulting in osteosclerosis and excessive fibrosis in the bone marrow cavity. Excessive osteoid accumulation at the endplate and fibrosis are histopathological hallmarks of high bone turnover bone disorder [34]. The persistent elevated serum PTH dysregulated bone remodeling by activated osteoclastic resorption [35], which induced bone loss and extraosseous calcium deposition.

Chronic Inflammation

Chronic inflammation, such as that observed in patients with systemic lupus erythematous and rheumatoid arthritis, activates osteoclastic resorption. Chronic inflammation is characterized by disturbance of cytokine levels; intestinal absorption of calcium, phosphate, and nutrients; fatigue; and vitamin D deficiency, which increase bone resorption and degree of osteoporosis [36]. Chronic inflammation increases resting energy expenditure (400–500 kJ/day) [37]. The increase of energy expenditure induced anorexia-relate hypovitaminosis, and the decrease in intestinal calcium uptake made the bone as the only source of plasma calcium [38]. Besides, glutathione depletion by chronic inflammation increased the oxidative stress in the intestine, which altered the transcellular and paracellular calcium absorption [39]. The increase of TNF, RANKL, and IFN-γ activates the calcium mobilization by downregulating the osteoblastic osteocalcin and activating the RANKL signaling [40–42]. In addition to cytokine secretion, inflammasome accumulation is associated with osteoclast activation. Persistence of inflammation increases intracellular calcium concentration to induce inflammasome assembly and activates the osteoclast [43–45]. In order to control the inflammation, high-dose glucocorticoid would be applied. However, excess glucocorticoids enhance bone resorption by reducing OPG expression, increasing RANKL expression and reactive oxygen species, and prolonging the life span of osteoclasts [46]. High-dose glucocorticoid increased the skeletal muscle wasting, which related to sarcopenia and immobility. Both sarcopenia and immobility inhibit the osteoblast survival and activate the osteoclast [47]. Therefore, involve-

ment of inflammation in osteoclast activation should be the main focus for treating osteoporosis.

Low Bone Turnover Disorders

Low bone turnover disorders include adynamic bone disease, osteomalacia, GIO, and liver cirrhosis. Low bone turnover disorder is characterized by decreased osteoid and osteoblast volume and increased mineralization lag time. Such pathologic hallmark is caused by the absence of osteoblast activity and osteoblast apoptosis [48, 49]. Medications such as bisphosphonates, excessive inhibition of PTH in patients with advanced CKD, and prolonged use of glucocorticoid worsen osteoblast apoptosis and suppress the osteoclast-mediated bone remodeling [50, 51].

Adynamic Bone Disease and Osteomalacia in CKD

Age, insulin resistance or diabetes mellitus, uremic toxin accumulation, and treatment-related factors (oral calcium-containing phosphate binder or excessive vitamin D analog usage) induce adynamic bone disease in patients with CKD [52]. In the early stage of CKD, accumulation of uremic toxins such as indoxyl sulfate suppresses the formation of mineralized bone nodules from osteoblasts [53] and simultaneously inhibits osteoclast-related bone resorption. Decelerated bone remodeling lessens the calcium uptake from osteoblast and increase the extraosseous calcium deposition in soft tissues. In order to prevent further extraosseous calcification, osteocyte secrets sclerostin [11]. However, increased sclerostin secretion decreases osteoblast activity by inhibiting the Wnt signaling pathway during osteoblast bone formation [54]. Sclerostin accumulation exacerbates PTH resistance. Persistence of PTH resistance increases the pentosidine-to-matrix ratio and decreases the crystallinity-deteriorated viscoelastic property of extracted long bones and bone strength [55]. In patients with advanced CKD receiving excessive active vitamin D, oversuppression of PTH decreases osteoblast activity. Excessive use of aluminum-containing phosphate binders also decreases osteoblast activity because of the intestinal absorption of aluminum [56]. In summary, adynamic bone disease in CKD is multifactorial, and the bone formation is suppressed profoundly.

Glucocorticoid-Induced Osteoporosis (GIO) (Fig. 30.2)

High bone turnover occurs in the initial phase of GIO because of the steroid direct effect. However,

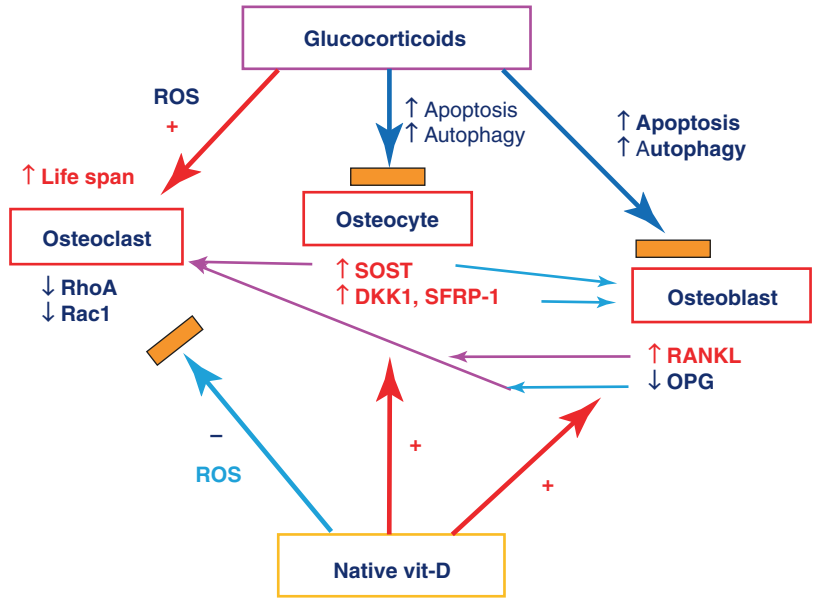

Fig. 30.2 The mechanism of low turnover bone disorder: Glucocorticoid-induced osteoporosis as example [12]

they also suppress the bone-degrading capacity of osteoclasts by disturbing the organization of the cytoskeleton and suppresses the osteoclast-mediated bone formation [46, 57]. Prolonged use of glucocorticoids decreases bone resorption [58], which is mainly characterized by low bone turnover disorder [59]. Glucocorticoids inhibit bone formation through several mechanisms: (1) by inhibiting mesenchymal stem cell differentiation into osteoblasts through PPARγ2 [60]; (2) by inhibiting Wnt/β-catenin signaling by enhancing Dickkopf expression and by maintaining GSK 3-β expression [61]; (3) by inhibiting type I collagen synthesis from osteoblasts [62]; (4) by arresting M-CSF activation of RhoA and Rac1 of osteoclast cytoskeleton[57]; and (5) by inducing osteoblast apoptosis by activating caspase 3 [63]. Increase in the duration of glucocorticoid exposure decreases bone turnover rate by inducing osteoblast apoptosis [64] resulting in decrease bone formation. Moreover, intermittent PTH secretion improves bone remodeling and bone formation in patients with GIO-related low bone turnover disorder [65].

Bone Quality Loss

Bone is composed of inorganic minerals (mainly calcium and phosphate hydroxyl apatite crystals) and type I collagen [66]. Deterioration of the structural arrangement and orientation of bone minerals because of a metabolic disorder decreases bone quality, which increases bone fragility without inducing a severe loss of bone quantity [67]. Animals with high and low bone turnover disorders have lower material-level bone toughness compared with normal animals. This indicates that skeletal pentosidine-to-matrix ratio is increased in advanced CKD and that this increase is independent of the bone turnover rate and inversely associated with a decrease in kidney function. Although hydration changes occur in patients with both high and low bone turnover disorder, data suggest that nonenzymatic collagen cross-links may be a key factor in compromising the mechanical properties of patients with CKD. [68]. Results of a dynamic study on the mechanical properties of the femur assessed using a dynamic mechanical analyzer [69] showed that both low and high bone turnover disorders are associated with poor bone quality.

In summary, the characteristics of low bone turnover disorder are inhibited osteoblast formation, and restoration of osteoblast viability in addition to treatment for the underlying disorder is crucial.

Bone Mineral Density in Patient with CKD

Relationship Between BMD and Renal Osteodystrophy

Renal osteodystrophy (ROD) includes a variety of bone lesions that differ in both mechanisms of development and therapeutic approaches. The TMV (turnover, mineralization, and volume) system is a recently developed, simple, and clinically comprehensive system to classify CKD-MBD [19]. The TMV system provides information on the range of pathologic abnormalities that can occur in CKD patients. Bone turnover and bone volume can be classified as high, normal, or low. Bone mineralization is classified as normal or abnormal. The Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines distinguish the following six types of bone disorders on the basis of TMV system: hyperparathyroid bone disease (high turnover, normal mineralization, and any bone volume), mixed bone disease (high turnover with mineralization defect and normal bone volume), osteomalacia (low-turnover bone with abnormal mineralization and low-to-medium bone volume), adynamic bone disease (low-turnover bone with normal mineralization and low or normal bone volume), amyloid bone disease, and aluminum bone disease [20–22].

The types of bone histology depend on the degree and duration of renal impairment, patient age and comorbidities, mode and years of dialysis, associated medications for hyperparathyroidism, serum calcium and phosphate levels, etc. In addition to ROD, these patients are also more

likely than the general population to have osteoporosis, which is also influenced by age, gender, menopausal status, drugs, nutrition, and exercise [23]. Thus, it is difficult to separate these disease entities clinically.

The most common high turnover abnormality in ROD is hyperparathyroid bone disorder (HPBD; osteitis fibrosa cystica: OFC) with excessive osteoclastic bone resorption and bone marrow fibrosis [24]. HPBD may present with several types of radiographic findings. Due to increased osteoclastic activity, bone resorption may occur in many skeletal sites, including subperiosteal, intracortical, endosteal, trabecular, subchondral, and subligamentous, etc. [25]. Subperiosteal bone resorption most commonly occurs in the phalanges, humerus, and distal epiphyseal region of clavicles [26]. Subchondral resorption in sacroiliac joints may lead to "pseudo-widening" of the joint. Losses of lamina dura of the teeth are also common in SHPT patients [25]. Excessive osteoblastic activity may follow as compensation for the bone resorption, with resultant osteosclerosis [25], which is commonly seen in most sites of axial skeleton, including the pelvis, ribs, spine, and skull. Excessive osteoid accumulation below the endplates of vertebral bodies occurs, and with normal density in the middle parts, these vertebral bodies appear under radiological films as "rugger jersey spine sign" [27]. Excessive terminal phalange resorption may result in a deformity known as acroosteolysis [25]. Brown tumors, known to be caused by rapid osteoclastic activity and peritrabecular fibrosis, may affect pelvis, ribs, and clavicles and sometimes may result in pathological fractures. Brown tumors of vertebral column may also present with spinal cord compression [28, 29]. Metastatic calcification, a result of increased calcium/phosphate solubility product in extracellular fluid [30], is responsible for the vascular calcification in SHPT patients. Metastatic calcifications mostly affect the hips and shoulders, although other joints may also be affected [31, 32].

Low-turnover bone diseases include osteomalacia, aluminum-induced bone disease, and adynamic bone disease (ABD). Osteomalacia alone is an uncommon presentation in HD patients [33]. This mineralization defect is related to reduced 1,25-dihydroxyvitamin D (1,25D) and chronic metabolic acidosis [34]. Aluminum ingestion causes a mineralization defect, markedly reduces both osteoclast resorption and osteoblast surface, and is associated with the low-bone turnover disease osteomalacia. Chronic low-dose aluminum exposure with high intake of vitamin D in dialysis patients reduces parathyroid hormone synthesis and secretion, even in the presence of hyperphosphatemia; these patients may present with adynamic bone disease rather than osteomalacia [35]. The prevalence of aluminum-related bone disorders has been reduced over recent decades due to emergence of nonaluminum-containing dialysate solutions and phosphate binders [36].

CKD Progression and BMD Changes

Low BMD in CKD Not Yet Receiving Dialysis

With progressive decline in renal function, CKD patients suffer from hyperparathyroidism secondary to a decrease in serum calcium, a reduction in 1,25D (calcitriol) synthesis, and/or impaired phosphate excretion. The cloning of klotho and fibroblast growth factor 23 (FGF-23) has enabled the progressive unraveling of their roles in calcium/phosphate metabolism over the past decade. Progressive P accumulation leads to increases in serum PTH and FGF-23, both of which play important roles in consequences like renal osteodystrophy, hyperparathyroidism, calcemic uremic arteriopathy, and uremic cardiomyopathy.

Normal serum phosphorus and calcium levels are maintained by the integrative actions of PTH and 1,25 D. The phosphatonin FGF-23 directly controls renal phosphorus excretion and, along with the aforementioned hormones, plays a role in regulating systemic mineral metabolism. FGF-23, a 25-amino acid protein, prevents renal phosphate reclamation by decreasing the type 2a sodium-dependent phosphate cotransporters (NaPi-2a) expression in PCT. FGF-23 also suppresses the

expression of 1α-hydroxylase, the enzyme that converts 25D to calcitriol, resulting in decreased renal production of activated vitamin D [37–39]. FGF 23 and FGF receptor interaction is facilitated by the coreceptor Klotho [40]. Serum FGF-23 levels are found to be increased as early as CKD stage 3, which helps to keep serum P within the normal laboratory range. FGF-23 may also be responsible for early reduction in calcitriol levels during early CKD [41–43]. These findings indicate that clinical strategies to decrease FGF-23 may be therapeutically useful for normalizing calcitriol levels in these patients. Hasegawa et al. [44] found significantly increased FGF23 levels in CKD rats as compared with the normal rats, as early as 10 days after kidney destruction, preceding the rises of phosphate and creatinine. The factors that lead to this early FGF23 elevation are unknown.

Further loss of renal tissue leads to reduced Klotho expression, resulting in FGF resistance and correspondingly increased serum FGF level. This frequently occurs in stage 4 and 5 CKD, when hyperphosphatemia persists despite marked elevations of FGF-23 and PTH [45]. Hyperphosphatemia eventually becomes clinically significant due to many factors, including diminished nephron mass [46], FGF-23 resistance, and reduced calcitriol synthesis. The accumulated P combined with Ca results in calcium phosphate crystal deposition in soft tissue. Hypocalcemia, hyperphosphatemia, and low calcitriol levels all stimulate PTH formation and secretion, known as secondary hyperparathyroidism [47]. Excessive skeletal remodeling occurs in secondary hyperparathyroidism during progressive CKD, resulting in excessive bone resorption, defective bone formation, and abnormal mineralization. Finally, defective bone mineralization with heterotopic mineralization or metastatic calcification occurs in blood vessels and heart tissue, also known as calcific uremic arteriolopathy (CUA) [48, 49].

Patients with CKD have reduced BMD due to multifactorial causes, including acid-base disturbances, and impaired vitamin D and PTH homeostasis. Chronic metabolic acidosis in CKD patients may increase bone resorption due to bone buffering and slow dissolution of bone mineral [50]. Bone biopsies of mild to moderate CKD patients reveal PTH excess and increased bone turnover [51]. Bone turnover markers have been found to correlate with PTH levels and GFR [52], and low calcitriol level is found to be an independent risk factor for hip fractures [8]. Although many studies reported a decrease BMD in CKD patients, the exact relationship between BMD and CKD was still unclear due to study limitations [53]. In the Third National Health and Nutrition Examination Survey (NHAHES-III) Study, subjects with worse renal function had significantly lower femoral BMD; however, this association was explained by confounding factors, like age, sex, ethnicity, etc. Renal function itself was not found to be independently associated with BMD after taking sex, age, and body weight into account [54].

Influence of Comorbidities

CKD is a complex comorbid condition with a multiplicity of clinical manifestations. It is closely linked with cardiovascular disease and associated with a very high mortality rate. In the United States, CKD consumes about one-third of Medicare expenditures. Comorbid conditions of CKD include hypertension, diabetes, dyslipidemia, cardiovascular disease, anemia, and bone and mineral disorders. Changes in mineral metabolism with alterations of hormonal regulation have recently been found in CKD, associated with various forms of bone diseases; this has become known as the kidney-bone axis. During the past decade, investigators have focused more on the bone-vascular axis and the relationship between mineral metabolism disorders and soft tissue and cardiovascular calcifications.

The complex pathophysiologic mechanisms of arterial calcification include disturbances of mineral metabolism and mineral-regulating proteins. Longitudinal population-based studies reveal an association between progressive vascular calcifications (VC) and bone demineralization. In dialysis patients, coronary artery calcification score was found to be inversely correlated with vertebral bone mass. In other words, increasing arterial stiffness coexists with pro-

gressive bone loss, which is responsible for most of the cardiovascular events in CKD patients. Vascular calcification is an active process involving various proteins that are similar to those involved in bone and mineral metabolism [55, 56]; this process represents a part of CKD-mineral and bone disorder [19].

Risk factors for premature VC in end-stage renal disease (ESRD) patients differ from the traditional atherogenic risk factors. Hyperparathyroidism and alterations in Ca-P mineral metabolism, especially hyperphosphatemia, modulate both renal osteodystrophy and vascular calcification [57, 58]. An association has been observed between extraosseous calcifications and hyperparathyroidism [59, 60] and reversal of extraosseous calcifications with reduction of bone turnover after parathyroidectomy [61–63]. In contrast, one study described an association between low bone turnover and vascular calcifications [64]. Therapeutic measures for SHPT—like PTX and excessive calcium or aluminum load, which lead to lower bone turnover and adynamic bone disease—may also influence the development of arterial calcification [64]. A recent study carried out by Asci et al. [65] on 207 CKD stage 5 regular HD patients revealed an association between bone turnover, bone volume, and coronary calcifications. After adjusting for traditional risk factors (e.g., age, gender, DM, smoking, serum lipid, history of CVD, and hs-CRP), they found that low bone turnover was negatively correlated with coronary artery calcification (CAC), high bone turnover was positively correlated with CAC, and no association was found between normal turnover and CAC [65]. Age is a known risk factor for cardiovascular calcification in both general populations [67] and HD patients, and an interaction between cancellous bone volume and age was also found to be associated with CAC [66]. Thus, in addition to the demonstrated nonmodifiable risk factors (age, sex, diabetes mellitus, and HD duration), bone turnover and bone volume should also be considered as nontraditional risk factors that may influence CAC.

Diabetic ESRD patients tend to present with adynamic bone disease with or without aluminum deposition [68, 69], whereas present with hyperparathyroid bone disease in less than 10% of cases [70]. Bone resorption markers like serum tartrate-resistant acid phosphatase (TRAP) and urinary hydroxyproline are increased, especially when associated nephropathy develops. Insulin plays a role in bone anabolism through the insulin-like growth factor 1 (IGF-1) pathway. Patients with type 1 diabetes mellitus (DM) with true insulin deficiency may exhibit more bone loss than type 2 DM patients, in whom serum insulin levels are increased due to tissue resistance. Although bone mass can remain high in type 2 DM patients, bone quality is impaired due to accumulation of advanced glycation end products (AGE) in collagen. Increased bone fragility may also result from low bone turnover, reduced unmineralized bone matrix, and increased collagen glycosylation [71, 72]. Thus, bone density in these patients may not predict increased bone fragility [73]. Furthermore, diabetic ESRD patients often have other risk factors for fractures, including longer diabetes duration, diabetic retinopathy, neuropathy, and insulin treatment [74–77]. The regular oral hypoglycemic medications may also play a role in bone loss in these patients.

Metabolic syndrome (MS) is also associated with low bone mineral density (BMD) in patients with chronic kidney disease. Studies have shown that in both MS group and non-MS groups, BMD was negatively correlated with age, hemodialysis period, and PTH [78, 79].

Influence of Treatments (Medications) on CKD-Related Osteodystrophy

Drug-induced osteoporosis is an important consideration in CKD patients. Unfractionated heparin (UFH) is the most common anticoagulant used in hemodialysis units, due to its relative ease of use, safety, and low cost; however, it is associated with many known side effects, such as heparin-induced thrombocytopenia, hypertriglyceridemia, and hyperkalemia. It is unclear whether intermittent heparin use is related to low bone mineral density, since most dialysis patients have other associated risk factors for osteoporosis, like diabetes mellitus, secondary hyperparathyroidism, old age, and physical inactivity.

Therefore, UFH is only replaced with other anticoagulants (e.g., direct thrombin inhibitors, citrate dialysate, and heparin-free dialysis) when other complications develop, such as heparin-induced thrombocytopenia. A study conducted by Grzegorzewska et al. [80] revealed that dialysis patients who receive regular LMWH, antiplatelet agents, or both, show lower bone mineral density in the femoral neck, but results of larger clinical trials are pending.

In diabetic CKD patients, skeletal effects of pharmacological treatments of type 2 diabetes also play a role in determining BMD. Biguanides like metformin increase the differentiation of bone marrow mesenchymal stem cells (MSC) into osteoblasts through the transactivation of Runt-related transcription factor 2 (RUNX2), resulting in increased bone formation. Glitazones, by simultaneously activating peroxisome proliferator-activating receptor γ (PPARγ) and inhibiting RUNX2, shift MSCs toward the adipocyte lineage, resulting in a reduced osteoblastic lineage [81].

Glucocorticoids are the drugs that most often cause osteoporotic fractures in both general and ESRD populations. Other medications have also been proven to be associated with bone loss, including calcineurin inhibitors, antiretroviral drugs, selective inhibitors of serotonin reuptake, anticonvulsants, loop diuretics, oral anticoagulants, and proton pump inhibitors. Cyclical hormone replacement therapy (HRT) may maintain BMD in postmenopausal women with secondary amenorrhea after dialysis [82]. Therapeutic measures like continuous hormone-replacement therapy (HRT), bisphosphonates, and selective estrogen receptor modulators (SERMS) may improve BMD in normal renal function status, but their roles in ESRD patients are still unclear.

Influence of Age and Gender

As the average age of CKD and ESRD patients increases, age-associated osteoporosis is also increased in these patients, at a higher rate than in general population. Age is an independent factor associated with bone loss in CKD and ESRD patients. Protein malnutrition, inflammation, and glucose abnormalities are more frequent in older ESRD populations and are responsible for more BMD loss in this group compared with in younger patients. Postmenopausal osteoporosis is also a complication related to renal mineral and bone disorder. In a study including 112 postmenopausal hemodialysis patients, serum estradiol levels were found to be higher in hemodialysis patients than in those without CKD, and endogenous estrogen was found to play a role in preventing bone loss in postmenopausal hemodialysis women [83]. Many studies have found a high prevalence of calcidiol deficiency and insufficiency in predialysis patients, regardless of geographic location. A significant inverse correlation between calcidiol and parathyroid levels has also been noted in both general and predialysis populations, but the underlying mechanism underlying calcidiol deficiency is unknown [84].

Decreased physical activity may be associated with loss of bone strength in dialysis populations, and a rehabilitation program may play an important role in preventing this problem. Not only high impact activities have been proven osteogenic [85], but low-impact activities, like moderate intensity walking may also increase lumbar BMD [86]. Since CKD and ESRD patients are prone to fatigue and generally have a lower exercise capacity, low-impact activities are more favored in this population. A recent study revealed that active ESRD patients with adynamic bone disease have greater mineralized bone volume than less active patients [87]. Human studies including hemodialysis patients show a correlation between muscle strength and BMD [88]. The mechanical load applied by the muscle on bone is directly responsible for bone formation and remodeling [89]; therefore, simple, low-impact, weight-bearing exercises, such as walking and resistance exercise (strength training), are encouraged as daily physical activities in CKD patients to improve BMD.

Dialysis Modalities on BMD

BMD in Hemodialysis Patients

Even before dialysis, CKD patients with lower GFR (with or without higher iPTH values)

present with lower BMD [90]. Prospective studies have revealed both gain and loss of BMD after the initiation of dialysis [91, 92], with increased dialysis associated with increased fracture risk. In HD patients, factors influencing low BMD include age, gender, lower body weight, and higher level of parathyroid hormone [93]. Compared with a general population, a dialysis patient population showed a 4.4-fold greater relative risk for hip fracture and a 2.4-fold higher mortality rate [11]. Risk factors like female gender, lower BMI, and white race influence hip joint fractures in the general population; however, in dialysis patients, lower serum iPTH values may indicate a greater risk of hip fractures [11]. Dialytic male patients seem to have higher risk of vertebral fractures, which is predicted by both BMD (a doubling prevalence for each 1-SD reduction in lumbar spine BMD) and by iPTH values [94]. Lower serum iPTH values are also associated with higher vertebral fracture prevalence; the serum iPTH values that predict the lowest fracture prevalence seem to be approximately one to three times the upper normal range [94].

Overall, osteoporosis is prevalent in hemodialysis patients. A cross-sectional study of hemodialysis patients using bone biopsy and histomorphometric analysis showed that hemodialytic osteoporosis patients have a low bone formation rate with normal bone eroded surface (BFR/BS), even with normal bone resorption. The results of this study are also alarming due to the fact that osteoporosis, a common disorder of aging, was determined to be prevalent in younger dialysis patients [95]. Cytokines that play roles in bone remodeling, like OPG, soluble receptor-activator of NF-κB ligand (sRANKL), and TNF-α, are also involved in the mechanisms of osteoporosis, in addition to many other traditional risk factors [95].

BMD in Peritoneal Dialysis Patients

The nature of bone disease differs in peritoneal dialysis (PD) patients and HD patients, since different factors influence calcium, phosphate, and PTH metabolism between the two modules. PD patients have better phosphorus clearance, higher removal of transferrin-bound aluminum, higher intake of phosphorus due to the recommended high protein diet, and higher bicarbonate loss than HD patients; they are also used to experiencing a constant glucose load and constant calcium load with regular or high calcium solutions [96]. PD patients are also more frequently associated with adynamic bone lesions (61% in PD patients vs. 36% in HD patients) [97, 98]. In PD patients, low BMD indicates poor outcome, since predictors of low BMD (age, poor nutrition status, metabolic acidosis, high phosphorus, anemia, etc.) are associated with worse prognosis in PD patients [99]. Low body weight seems to be the most important risk factor for osteoporosis in chronic PD patients [100]. Insufficient dialysis dose and older age also play an important role in osteoporosis of those patients. A recent cross-sectional study conducted by Jeong et al. evaluated the risk factors associated with BMD in chronic PD patients. Traditional markers of bone turnover (e.g., iPTH, 25D, osteocalcin, bone alkaline phosphatase, and serum C-telopeptide) were not associated with BMD in PD patients, whereas nutritional markers (e.g., prealbumin, nPNA, and BMI) predicted BMD in chronic PD patients [101].

Secondary Hyperparathyroidism and Renal Osteodystrophy

The Pathophysiology of Secondary Hyperparathyroidism (SHPT)

As the glomerular filtration rate decreases in CKD progression, phosphate begins to accumulate due to the decrease in the functional nephron number. In addition, 1,25D produced in the remaining kidney is decreased, and renal 1α-hydroxylase activity is further inhibited by FGF-23 and other uremic factors that lead to 1,25D deficiency. Both phosphate burden and 1,25D deficiency cause hypocalcemia and stimulate PTH secretion from PTG, called SHPT. The PTH synthesis, transcription, and parathyroid

cell proliferation are mainly regulated through serum calcium and 1,25D level. Both hypocalcemia and 1,25D deficiency among CKD patients result in PTH secretion and PTG hyperplasia [22] and consequently result in unbalanced bone remodeling, soft tissue/vascular calcification, and increases the risk of cardiovascular event and all-cause mortality [23–26]. Recently, evidence has emerged supporting the role of FGF-23 as the primary event in the pathogenesis of SHPT. Administration of the FGF-23 antibody can markedly increase 1α-hydroxylase expression in kidney, which means that it can restore 1,25D levels significantly [27, 28]. These findings suggested that the increase of FGF-23 may be the principal mechanism behind reduced 1,25D levels in early CKD.

As hypocalcemia, 1,25D and 25-hydroxyvitmain D (25D) deficiency worsen in CKD progression, a general increase in the total number of parathyroid cells with a normal lobular structure occurs called diffuse hyperplasia. After progressing into the end stage of renal disease or even dialysis-dependent status, SHPT becomes more severe and PTG becomes grossly enlarged and exhibits some nodular formation (nodular hyperplasia) (Fig. 30.3). In advanced SHPT, the multi-nodule may develop into a single large nodule [29]. Once nodular hyperplasia in SHPT is established, these glands might be refractory to medical treatment, and surgical parathyroidectomy is indicated [30]. Hyperphosphatemia is a main risk factor aggravating the severity of PTG hyperplasia, and dialysis vintage and serum PTH level are also in a relation with nodular hyperplasia [31].

Pathophysiologically, hyperplasia precedes the decrease in CaSR expression. The decrease in vitamin D receptor (VDR) is parallel to the increases in hyperplastic growth and contributes to decrease the induction of the CaSR by VDRA [32, 33]. Downregulation of CaSR may be attributed by parathyroid cell hyperplasia, but not uremia per se [33]. Inadequate CaSR and VDR density in PTG cause the poor response of extracellular calcium to suppress PTH and failure of calcitriol (1,25 D) in treating SHPT. In general, parathyroid hyperplasia presents in CKD stage 5 patients with PTH > 400 ng/mL [34]. A PTG weight over 500 mg predicted nodular hyperplasia, and this is equivalent to an estimated value of 330 mm^3 [35]. In addition, a PTG volume > 300 mm^3 or maximum diameter > 8 mm predicted nodular hyperplasia [36, 37]. Furthermore, a PTG volume > 500 mm^3 or maximum diameter > 10 mm might be refractory to the calcitriol treatment to SHPT.

Impact of SHPT on BMD

Increases in bone marrow fibrosis and both osteoblastic and osteoclastic activity occur in progressive SHPT. With increased bone resorption and defective mineralization, the resultant cortical bone thinning may lead to bone pain and/or pathological fractures. These types of high turnover bone lesions, including osteitis fibrosa and mixed uremic osteodystrophy, are common in patients with serum intact PTH levels over 400 pg/mL. The resultant increased bone remodeling may lead to reduced bone mineral density. The radius bone considered to be the site that correlates best with serum PTH levels in long-term dialyzed patients. In a prospective study of vitamin D deficiency and SHPT, high serum PTH was a significant predictor of mortality [102].

Vitamin D Deficiency in Bone Loss

The Alteration of Vitamin D Metabolism in CKD

Decrease Vitamin D Synthesis and Increase Vitamin-D Catabolism in CKD

In CKD, PTH synthesis is increased in response to both 1,25D deficiency and hypocalcemia, and then PTH stimulates renal CYP27B1 expression to rescue the 1,25D level. 1,25D consequently induces VDR-mediated intestinal calcium absorption to keep calcium homeostasis. PTH also downregulates renal CYP24A1 mRNA transcription, a 24-hydroxylase enzyme responsible for vitamin D degradation, and leads to

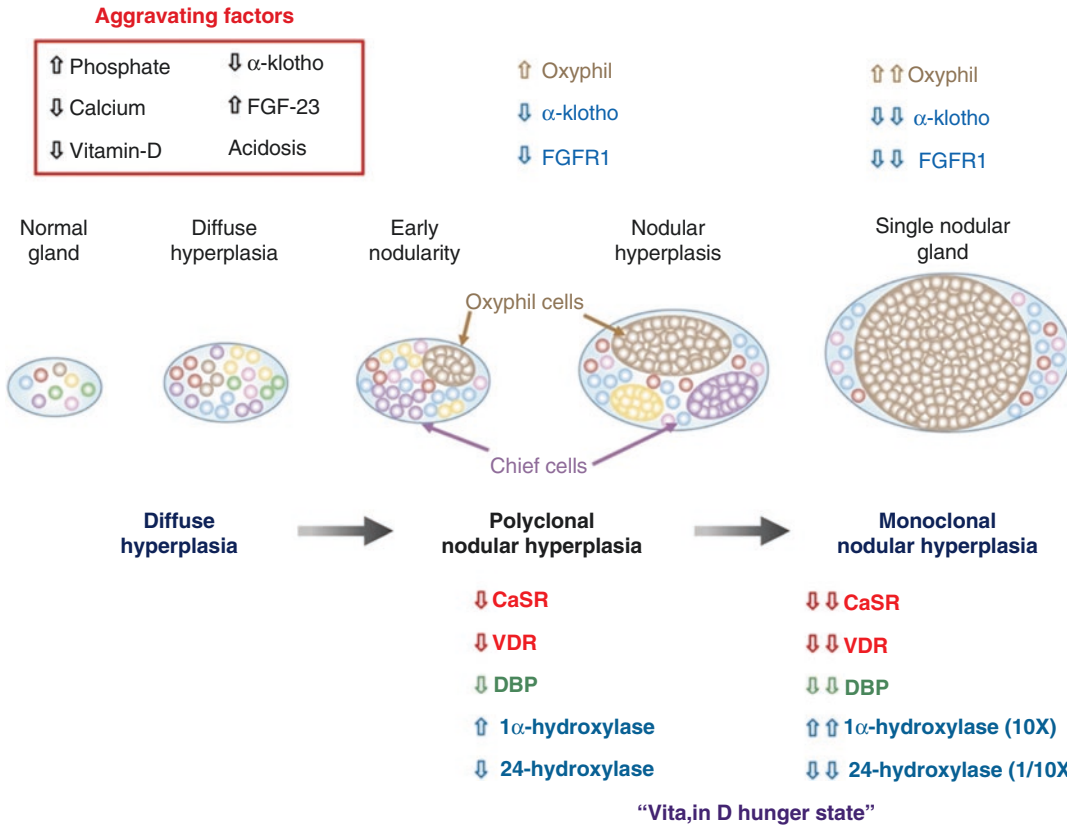

Fig. 30.3 The development of parathyroid gland hyperplasia in secondary hyperparathyroidism (SHPT). In advanced SHPT, monoclonal cell growth vigorously that occupy the most of the gland and form a single large nodule. Both α-klotho and FGFR1 expression on parathyroid cells are decreased during the progress of hyperplasia and are negatively correlated with the volume of the hyperplastic parathyroid tissue. The reduced VDR and CaSR expression is prone to nodular hyperplasia and is considered to be in a relation to calcitriol or calcimimetics resistant. Increased 1α-hydroxylase and decreased 24-hydroxylase expression in secondary hyperplasia PTG cells would highlight the requirement of more 25D in SHPT. In parathyroid cell, the translocation of vitamin D from cytosol into mitochondria for 1,25D synthesis with the help of cytosolic DBP, and reducing the cytosolic DBP content within oxyphilic cell predominant parathyroid nodules might decrease the amount of local intracellular 1,25D production. This hydroxylase enzyme and cytosolic DBP change highlight the requirement of more 25D in SHPT, called vitamin D hunger. Increasing the serum level of 25D increases the intraparathyroid free and bound 25D levels, which might overcome the decreased DBP levels, and improve the vitamin D hypo-responsiveness state in PTG among SHPT patients.(Abbreviation: SHPT secondary hyperparathyroidism, FGFR1 fibroblast growth factor receptor 1, VDR vitamin D receptor, CaSR calcium sensing receptor, 1,25D 1,25-dihydroxy vitamin D, PTH parathyroid hormone, PTG parathyroid gland, VDD vitamin D deficiency, DBP vitamin D binding protein, 25D 25-hydroxy vitamin D) [70]

attenuating 25D and 1,25D degradation via the cAMP/PKA signaling pathway [61, 62].

As PTH controls blood calcium to keep serum calcium homeostasis, FGF-23 regulates the serum phosphate level and is involved in vitamin D metabolism. Hyperphosphatemia can induce osteocytes and osteoblasts to express FGF-23 and subsequently reduces phosphate reabsorption by inhibiting NaPi-IIa activity directly and indirectly by inhibiting renal CYP27B1 expression to lower blood 1,25D level, then reduces intestinal phosphate absorption [63]. Additionally, FGF-23 induces renal CYP24A1 expression to degrade 25D and 1,25D levels [62].

The function of PTH and FGF-23 in regulating CYP27B1 works in a reciprocal manner and

competes with each other on CYP27B1 transcription. The direct administration of recombinant FGF-23 or its overexpression in mice induces a dose-dependent decrease in renal CYP27B1 mRNA expression, an increase in renal CYP24A1 mRNA expression, and a consequent decrease in serum 1,25D concentrations [28]. Instead, the administration of FGF-23 antibodies can increase renal CYP27B1 mRNA and decrease renal CYP24A1 mRNA to restore serum 1,25D concentration to normal. These changes are followed by increased serum calcium level, leading to decreased serum PTH [27]. Hence, FGF-23, rather than PTH, is a primary factor accounting for inappropriately low serum 1,25D concentration in CKD since the early stage of CKD. In brief, an increase of FGF-23 in CKD follows 1,25D deficiency and hypocalcemia, thereby increasing the PTH level and results in SHPT in CKD. The FGF-23 action may aggravate VDD if concurrently used with calcitriol or VDRA analogs during SHPT treatment as both FGF-23 and VDRA analogs both downregulate CYP27B1 and upregulate CYP24A1 expression to degrade 25D and 1,25D.

There is also another metabolic factor commonly presented in CKD that disturbs CYP27B1 expression such as diabetes [64], acidosis [65], and hyperuricemia [66, 67]. Therefore, high FGF-23 and CKD-related metabolic factors are associated with CYP27B1 transcription inhibition in CKD.

Lower 25D bioavailability in CKD is also another cause of VDD. As limited sun exposure and dietary vitamin D intake, less 25-hydroxyvitmain D filtered by declining GFR, diminished megalin expression, and albuminuria increase filtered 25-hydroxyvitmain D lost in urine are all aggravating factors that lead to 25D shortage and cannot provide an inadequate substrate for 1α-hydroxylase and worsens VDD in CKD [46, 68].

Nutritional Vitamin D Hunger in the Parathyroid Gland

In normal physiological conditions, FGF-23 can directly suppress PTH production by directly inhibiting PTH transcription and secretion and indirectly by increasing parathyroid 1α-hydroxylase activity [69]. FGF-23 can also increase CaSR and VDR expression and decrease PTG volume. However, low PTG α-Klotho and FGFR1 expression lets FGF-23 lose its inhibitory effect on parathyroid cells and fails to increase CaSR and VDR [70]. Moreover, the administration of FGF-23 in CKD animals cannot reduce the PTH level, which indicates FGF-23 resistance in PTG caused by the low expression of α-Klotho and FGFR1 [71]. In summary, in patients with CKD, FGF-23 levels increase progressively to compensate phosphate retention, but the high FGF-23 levels fail to suppress PTH secretion due to decreased Klotho-FGFR1 complex expression in hyperplastic PTG, called FGF-23 resistance. Furthermore, recent literature in dialysis patients of SHPT has shown that the expression of α-Klotho and FGFR1 is decreased in PTG of dialysis patients and were negatively correlated with the volume of the hyperplastic parathyroid tissue [71].

Compared with the normal gland, the mRNA expression and protein level for 1α-hydroxylase (CYP27B1) in secondary hyperplastic parathyroid cells is higher [73]. Increased 1α-hydroxylase (approximately tenfold) and decreased 24-hydroxylase (approximately 1/ten-fold) concentrations are found in 78% of secondary hyperplasia PTG cells and highlight the requirement of more 25D in SHPT [74]. The expression of 1α-hydroxylase is much higher in oxyphil cells than chief cells, which is the dominant cell group in SHPT. Calcimimetic treatment had a further 42% increase in parathyroid 1α-hydroxylase mRNA and 2.2-fold decrease in 24-hydroxylase mRNA that resulted in an ~53% decrease in PTH mRNA [75]. Besides, the decrease of megalin expression in the parathyroid gland may decrease 25D uptake and mediate the demand for more circulating 25D to correct PTH synthesis. Hence, the requirement for a substrate for vitamin D synthesis dramatically increases in SHPT and becomes hungrier if receiving treatment of calcimimetics in severe SHPT, called "vitamin D hunger status" as SHPT progresses in CKD. Therefore, more evidence in the data have overwhelmingly indicated the adjuvant role of

NVD in SHPT prevention and PTH lowering effect in combination with calcitriol or calcimimetics treatment.

Vitamin D Deficiency: Effect on Bone Quantity and Quality Loss

Vitamin D deficiency is a prevalent problem worldwide, including critically ill patients. Because vitamin D exerts multiple pleiotropic effects such as immunity, inflammation, cell proliferation, differentiation, apoptosis, and angiogenesis, there is growing evidence of a close relationship between vitamin D insufficiency and various systemic disorders [72]. Because vitamin D affects the interaction between osteoblasts, osteoclasts, and osteocytes, vitamin D deficiency is associated with insufficient bone mass or inadequate bone remodeling, which leads to fragile bones and increases the risk of fracture.

Vitamin D Deficiency and Bone Quantity Loss

Insufficient vitamin D is associated with low intestinal calcium absorption and sequential activation of PTH [73]. The histopathological characteristics of vitamin D deficiency with respect to loss of bone quantity include excessive nonmineralized bone matrix, a decrease in bone volume and premature bone formation. [74]. In low bone turnover disorder such as osteomalacia, the viability of mature osteoblasts decreased due to vitamin D deficiency [75]. Vitamin D deficiency is predictive of low BMD in both high and low bone turnover disease.

In high bone turnover disorder, lower serum vitamin D is related to severe inflammatory status and activated osteoclastogenesis. Low serum vitamin D concentration is associated with increased bone turnover and decreased bone volume in elderly people and postmenopausal women [76, 77]. In patients with ESRD, bone formation and trabecular mineralization are positively associated with serum vitamin D concentration independently of PTH or use of active vitamin D [90]. In patients with systemic lupus erythematous, low vitamin D concentration is associated with high disease activity and is a predictor of osteoporosis [78].

In the low bone turnover disorder, vitamin D deficiency reflects poor bone formation and osteoporosis. In patients with diabetes mellitus, the proportion with osteoporosis and osteopenia increases with a decrease in bone formation [79, 80]. In patients receiving long-term home parental nutrition, vitamin D insufficiency (<30 ng/mL) is predictive of femoral neck fracture [81].

Based on the data by the Institute of Medicine, a serum concentration of 25(OH) D higher than 20 ng/mL was sufficient for adequate bone health. However, the data from the National Health and Nutrition Examination Survey III revealed that such concentration was not sufficient for older people in bone health and falling prevention [82]. The serum concentration of 25(OH)D lower than 75 ng/mL was predictive to higher all-cause mortality, and such concentration should be optimal for falling prevention [83]. In summary, metabolic disease induces vitamin D deficiency, and such deficiency is associated with increased bone resorption, insufficient calcium–phosphate absorption, decreased osteoblast activity, and sequential loss in bone quantity.

Vitamin D Deficiency and Bone Quality Loss

Because bone is composed of calcium–phosphate hydroxyl apatite crystals and type 1 collagen, tissue mineral density and collagen cross-linking are associated with bone stiffness and strength. A disoriented arrangement of the crystals and collagen due to systemic illness affects bone formation, mineral deposition, and bone quality. Vitamin D affects gene expression in the ECM of bone, and insufficient vitamin D is associated with dysregulated arrangement of collagen and crystal. Progressive ankylosis protein, which is expressed in nonmineralizing tissue, is sensitive to VDRs and antagonizes mineralization in bone tissue. In VDR-knockout mice, activation of this protein maintains serum calcium concentration by enhancing bone resorption [84]. Higher mineral content with mature collagen and mineral constituents, which are observed in mature osteoblasts, results in more osteoids in vitamin D defi-

cient mice. Such crystallized osteoids hamper remodeling of the remaining bone tissue, causing the tissue to lose its resistance to fracture [85]. Patients with vitamin D deficiency may show disturbed microstructure and maturation of bone cells and weak bone strength, even if bone mass is maintained [86]. Although the direct effect of vitamin D on the interaction between osteoblasts, osteoclasts, and ECM needs further investigation, vitamin D deficiency is known to be associated with poor bone quality.

Role of Vitamin D Supplementation in High and Low Bone Turnover Disorders

Treatment of High Bone Turnover Disorder

Effect of Vitamin D Supplementation on Bone Quantity Loss (Fig. 30.4)

For the currently available medications for treating osteoporosis, the therapeutic window is dependent on the uncoupling between bone resorption and formation. During treatment with antiresorptive agents, inhibition of bone resorption precedes a later decrease in bone formation. For PTH treatment, the therapeutic window corresponds to the lag time required for increased bone formation to be coupled with increased bone resorption [87]. Because the balance of bone remodeling and formation requires the coupling of osteoblasts and osteoclasts, narrowing of the therapeutic window may be beneficial for maintaining bone quality and quantity simultaneously. In the high turnover bone disorders, the anti-resorption agent decreases bone resorption as the reflect by change of bone resorption markers, and it also couple with decrease the osteoblast viability, which was reflected by changing the serum bone formation markers. The therapeutic window would be the blue area in the Fig. 30.4a. In the high turnover bone disorders, adding nutritional vit-D on the anti-resorption agent will lessen the decreased bone resorption as the reflect by change of bone resorption markers, which means more old/fragile bone will be removed as blank areas "Φ" showed (Fig. 30.4b). Meanwhile, it also couple with slightly increase osteoblast viability, which would produce more good quality bone (blue area "Φ") as reflected by changing the serum bone formation markers. The therapeutic window would shift to right upperward when compared with Fig. 30.4a. Thus, during antiresorptive drug treatment for high bone turnover disorder, nutritional vit-D should be added.

Results of clinical trials have demonstrated that nutritional vitamin D supplementation maintains bone density and conjunctive use of vitamin D with antiresorptive agents increases treatment efficacy, and the effect on BMD was not inferior in comparison with active vitamin D supplement. In Chinese postmenopausal women, combination treatment with bisphosphonate and cholecalcif-

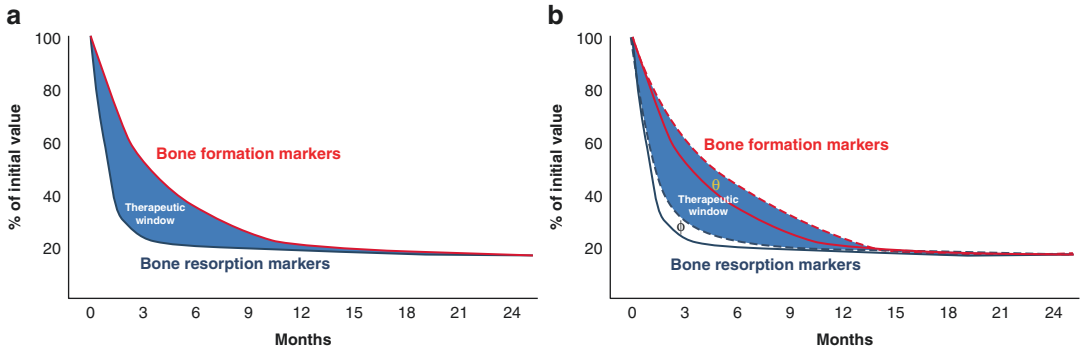

Fig. 30.4 Therapeutic window of anti-resorption drug for high bone turnover with osteoporosis (**a**) and the effect of adding nutritional vit-D (**b**) on the therapeutic window of anti-resorption drug [12]

erol increased lumbar BMD compared with that in women receiving a combination of bisphosphonate and calcitriol. Moreover, combination treatment with bisphosphonate and cholecalciferol results in a higher decrease in the levels of bone turnover marker than combination treatment with bisphosphonate and calcitriol [88]. Besides, the BMD-augmenting effect by cholecalciferol was dose-dependent. In patients with pediatric nephrotic syndrome, cholecalciferol supplementation improves BMD with dose-dependent effect [89].

In summary, when treating the high bone-turnover disorder, supplement of nutritional vitamin D with anti-resoptive agent is beneficial in maintaining BMD, and of its modulation on osteoblast and avoidance of oversuppression of osteoclast decreases the therapeutic window. In contrast to active vitamin D, the action of nutritional vitamin D on bone formation is dose-dependent.

Effect of Vitamin D Supplementation on Bone Loss: Bone Quality

Vitamin D supplementation plays an adjunctive or therapeutic role in treating quality bone loss. Khajuria et al. [90] found that alfacalcidol supplementation with bisphosphonates maintains bone mass and bone strength in ovariectomized rats with osteoporosis. Vitamin D3 and vitamin K supplementation attenuates detrimental damage induced by advanced glycosylate end products on osteoblasts by upregulating collagen expression [91]. However, the supplement of supraphysiologic active vitamin D abated the RANKL signaling and expression between osteoblast/osteoclast, and excessive intestinal calcium and phosphate absorption might influence the bone quality. Instead, cholecalciferol supplementation with a target level of up to 75 nmol/L, on the other hand, improves PTH level and muscle strength in a dose-dependent manner [92]. Nutritional vitamin D supplementation is helpful in maintaining bone microarchitecture in a dose-dependent manner. Tabatabaei et al. found that the architecture of long bones in guinea pig offspring improved more with higher maternal cholecalciferol supplementation [93]. Therefore, vitamin D supplementation should play a role in maintaining bone strength and architectural stability during osteoporosis treatment.

Extraskeletal Effect of Vitamin D in Treating Osteoporosis: Alleviating Inflammation and Oxidative End Products

Take estrogen-deficiency related osteoporosis as example in treating high bone turnover disorder (Fig. 30.5). Estrogen deficiency is associated

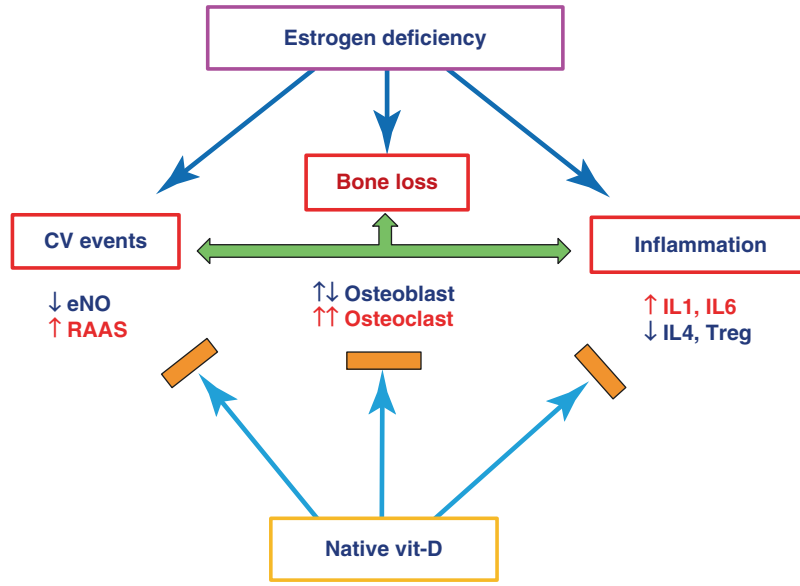

Fig. 30.5 Beneficial effects of vit-D on high bone turnover disorder treatment: menopause-related osteoporosis as example [12]

with bone loss, inflammatory status, and higher cardiovascular event due to dysregulation of the renin-angiotensin-aldosterone system (RAAS). Several lines of evidence suggest estrogen deficiency due to menopause may contribute to over activity of the RAAS. Animal models of estrogen deficiency also showed upregulated tissue expression of ACE and AT1R and decreased tissue expression of AT2R. The endothelial-derived nitric oxide (NO), synthesized by endothelial NO synthase (eNOS) from amino acid L-arginine and molecular oxygen, plays a pivotal role in maintaining vascular homeostasis and vasodilation. Animal study also showed ovariectomy downregulated cardiac eNOS gene expression. There are many cross talk between inflammation-bone loss-CV events in estrogen deficiency status. Vitamin D functions as an inflammatory modulator by affecting T cells. Low serum 25(OH)D3 level is associated with high systemic levels of inflammatory cytokines such as IL-6 or IL-1, which function as osteoclast stimulators [94]. 1α,25(OH)2D affects adaptive immunity by increasing the activity of type 2 T helper cells and decreasing the number of inflammatory type 1 T helper cells [95]. It also counteracts the overactivation of the RAAS and might decrease the incidence of cardiovascular events. Inflammatory cytokines directly increase osteoclast activity and bone resorption. Nutritional vitamin D alleviates renin-angiotensin-aldosterone activity, which may decrease endogenous NOS level and relieve oxidative stress [96]. On the other hand, the gut microbiota and increased gut permeability play in triggering inflammatory pathways that are critical for inducing bone loss in sex steroid-deficient mice. The probiotics that decrease gut permeability have potential as a therapeutic strategy for postmenopausal osteoporosis. Villa et al. reported that vitamin D supplementation improved femur and lumbar trabecular number in the offspring of pregnant rats by altering intestinal permeability and systemic lipopolysaccharide concentrations [97]. Therefore, vitamin D helps in treating osteoporosis by functioning as an anti-inflammatory modulator, which may improve excessive bone resorption.

Vitamin D for Treating Low Bone Turnover Disorder: Combination with Anabolic Agents

Low-energy bone fracture is common in patients with low bone turnover disorder such as GIO or prolonged bisphosphonate use [98, 99]. Nutritional vit-D treatment for GIO will not only decrease inflammation and oxidative stress on the osteoclast but also rescue the viability of osteocyte and osteoblast, which will recover the remodeling activity of the lower bone turnover states. In osteoporosis patients with low bone turnover, osteoanabolic agent therapy will increase bone formation and sequentially enhance bone resorption (Fig. 30.6a). The therapeutic window in this figure would be the blue color area. In osteoporosis patients with low bone turnover, adding nutritional vit-D on osteoanabolic

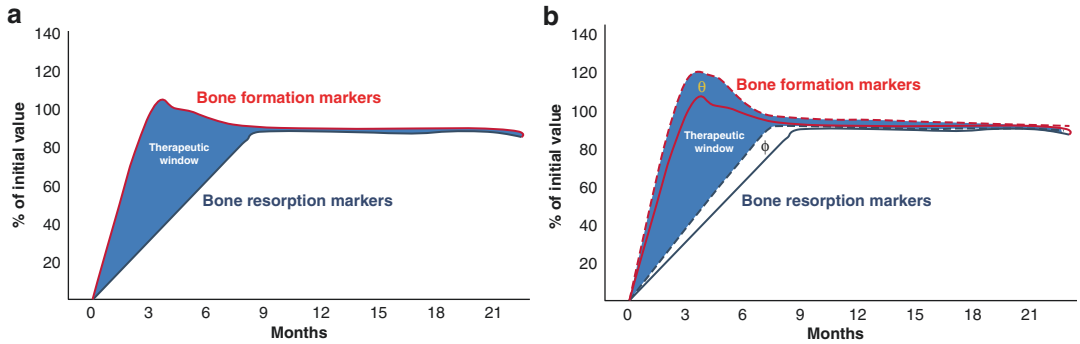

Fig. 30.6 Therapeutic window of anti-resorption drug for low bone turnover with osteoporosis (**a**) and the effect of adding nutritional vit-D (**b**) on the therapeutic window of anti-resorption drug [12]

agent therapy will further increase bone formation with osteoblast that may produce more good quality bone (Fig. 30.6b). It also will be sequentially further enhanced bone resorption, which will remove more old/fragile bone. The therapeutic window would shift to left upperward when compared with Fig. 30.6a. Thus, during antiresorptive drug treatment for low turnover bone disorders, nutritional vit-D should be added.

The rate of osteoblast survival is low, and sequential coupling of bone remodeling is abated in patients with low bone turnover disorder. Therefore, osteocyte/osteoblast apoptosis is common when using anti-resorptive agent alone [100]. From the EuroGIOP trial, bone-forming agents improved BMD and bone quality better than with treatment with bisphosphonate [101]. In HD patient with adynamic bone disease who received PTH analog treatment, 6 months of PTH analog improved, the bone formation rate was increased, and bone histopathology showed normal bone turnover [102]. Although recent meta-analysis reported a neutral effect on the vitamin D supplement for preventing fracture in a community-indwelling elderly, vitamin D deficiency was less common in such patients because the source of vitamin D was more diverse in community [103]. Therefore, physicians should be cautious while using pharmacological doses of active vitamin D for treating osteoporosis; moreover, nutritional vitamin D may be considered for treating low bone turnover disorder when treating with PTH analog in order to maintain the osteoblast viability.

Treatment of Osteoporosis: According to Bone Turnover (Fig. 30.7)

Preventing the bone loss in quality and quantity can be achieved by normalizing the bone remodeling process. Bone mass can be maintained using agents that decrease bone resorption, activate bone formation, or prevent osteoblast apoptosis. However, bone quality should be maintained using treatments based on the bone turnover rate. In patients with high turnover bone disorders such as PMO, RA, AS, COPD, or other chronic inflammatory disorders with the characteristic of

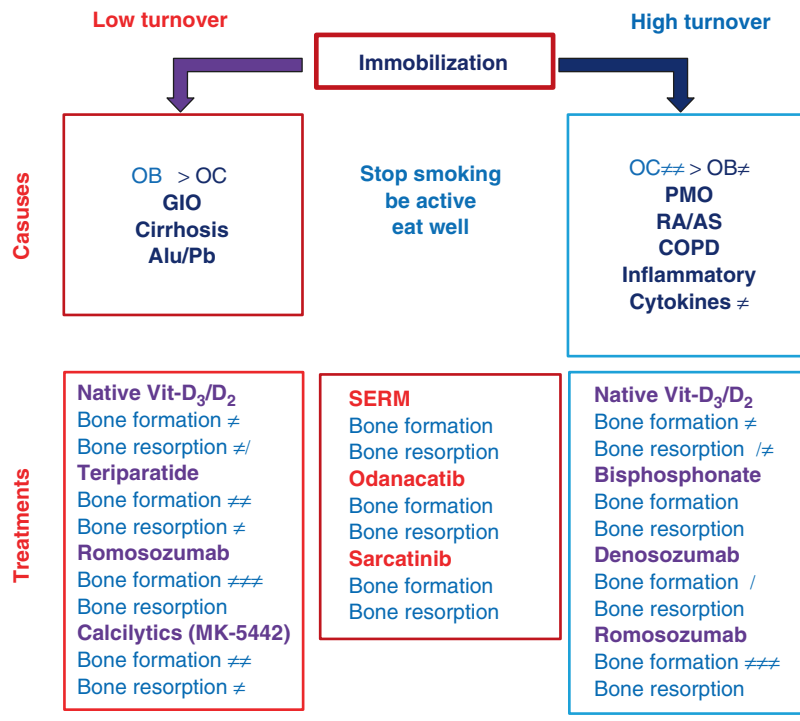

Fig. 30.7 Rational therapeutic consideration in osteoporosis: based on bone turnover rate [104]

higher osteoclast function than osteoblast, antiresorption medication such as bisphosphonate or denosumab could be considered. Other medication such as SERM, Odanacatib could be considered in special situations. In patients with immobilization, both increased osteoclast activity and decreased osteoblast viability were present. Choice of anti-resorption or osteoanabolic agent treatment should base on patient's bone remodeling status.

High Bone Turnover Disorder: Enhance Osteoclastogenesis Couple With More Increased in Osteoblast Viability

Antiresorptive Agents

Antiresorptive agents should be used for treating patients with osteoporosis having low bone mass. Widely used antiresorptive agents include bisphosphonates, calcimimetics, and denosumab.

Bisphosphonates

Bisphosphonates are the derivatives of inorganic pyrophosphates. Because of their high affinity to hydroapatite crystals in bone, bisphosphonates enter cells lining the surface of bone and prevent further cleavage by alkaline phosphatase. Moreover, bisphosphonates induce osteoclast apoptosis after they are taken up and metabolized into metabolites that interrupt the ATP generation [105]. It induces the osteoclast apoptosis rather than osteoclast progenitor cells, and bone formation may be abated by interfering the osteoblast viability and Wnt signaling [106, 107]. Well-established evidence is available on the use of bisphosphonates for treating osteoporosis in postmenopausal women and in patients with secondary hyperparathryoidism who show accelerated bone resorption due to osteoclast activation. Borah et al. reported that bisphosphonate treatment decreased fracture rate in patients with increased levels of serum bone turnover marker compared with that in patients with decreased levels of serum bone turnover marker [108]. In patients undergoing dialysis, bisphosphonate treatment decreases serum ionic calcium concentration; moreover, concurrent use of bisphosphonates with active vitamin D suppresses the aggravation of hyperparathyroidism [109]. If bisphosphonate is applied in low bone turnover disease, it indirectly inhibits bone formation by interfering with osteoblast viability, resulting in the occurrence of osteomalacia or fracture in atypical sites [106]. For example, patients with early stage CKD (stage II–IV) with more severe low bone turnover disorder, bisphosphonate treatment may inhibit bone turnover and adynamic bone disease [110]. Therefore, bisphosphonate treatment should be selected for patients with osteoporosis who have high bone turnover disorder and should be administered along with medications that maintain osteoblast viability.

Anti-RANKL Antibody

Denosumab. Denosumab is a monoclonal antibody that targets osteoclast-differentiation-inducing cytokine RANKL. It directly inhibits osteoclast activation and bone formation [87]. Moreover, use of denosumab induces the apoptosis of osteoclasts and osteoclast progenitor cells, which are the source of Wnt/β-catenin inhibitor [111]. Its application in the general population decreases the incidence of new vertebral, nonvertebral, and hip fractures. The efficacy of denosumab for decreasing the incidence of fractures is not inferior to that of bisphosphonates; moreover, denosumab maintains more BMD than bisphosphonates [112]. In patients with CKD, denosumab reduces fracture rate and increases BMD at all sites with respect to the different stages of eGFR [113]. Therefore, the use of denosumab can induce a mild positive balance in bone formation compared with the use of bisphosphonates [112].

Calcimimetics

Extracellular calcium concentration regulates PTH secretion through calcium-sensing receptor (CaSR), which is a G protein-coupled receptor. CaSR-induced activation of intracellular protein kinase C and mobilization of intracellular calcium from nonmitochondrial storage inhibit PTH secretion [114]. In patients with secondary hyperparathyroisim, calcimimetics may play a role in decelerating bone turnover and maintaining

BMD. CaSR affects osteoblasts by affecting RANKL/OPG signaling. In old animals, CaSR activation augments osteoblast-related bone formation by regulating the coupling between osteoblasts and osteoclasts, whereas in young animals, CaSR directly inhibits osteoclasts [115]. In patients with HD who have secondary hyperparathyroidism and increased baseline serum alkaline phosphatase levels, cinacalcet treatment increases BMD [116]. In patients undergoing dialysis and with secondary hyperparathyroidism, cinacalcet treatment for 6–12 months decreased serum PTH concentration and inhibited bone turnover rate [117]. The results of an EVOLVE study revealed decreased fracture rate in elderly patients receiving cinacalcet, with the relative hazard of fracture being 0.72 (95% CI, 0.58–0.90) [118]. Therefore, it would be applied in high bone turnover disorder.

Low Bone Turnover Disorder: Rescute the Osteoblast Viability: Anabolic Agents: PTH Analogs, Monoclonal Antibodies Against Wnt Pathway Inhibitors

Parathyroid Hormone

PTH activates the cyclic AMP-dependent protein kinase A and calcium-dependent protein kinase C signaling pathways to regulate osteoblast function. Moreover, it modulates the effect of IGF-1 and sclerostin [119]. Therefore, it should be applied as an anabolic therapy in patients with low bone turnover disorders. Subcutaneous teriparatide (recombinant 1–34 N-terminal sequence of human PTH) has been approved as an anabolic therapy. It decreases osteoblast apoptosis and activates dormant bone-lining cells to form active osteoblasts. Histomorphometric analysis showed increased trabecular bone volume, connectivity, bone microarchitecture, and bone trabecula number in elderly with osteoporosis [120]. In osteoporotic patients with normal PTH [77], subcutaneous teriparatide injection reduces the risk of vertebral or nonvertebral fractures. The efficacy of subcutaneous teriparatide injection for treating low bone turnover disorders such as adynamic bone disease or osteomalacia in patients with CKD has not yet been identified. However, in patients undergoing dialysis and with low bone turnover disorder, teriparatide supplementation increases the levels of bone turnover marker [121–123]. Even in the elderly with high bone turnover disease, there is an anabolic window after using PTH of 24 months [124] that allows the augmentation of bone formation rather than bone resorption. In patients with low bone turnover disorder such as GIO, teriparatide injection increases bone formation and corrects BMD [99].

Monoclonal Antibodies Against Wnt Pathway Inhibitors

Odanacatib and romosozumab are potential anti-osteoporotic agents against Wnt signaling pathway inhibitors [125, 126]. As mentioned previously, Wnt/β-catenin signaling is crucial for osteogenesis. Inhibitors such as sclerostin and DKK1 decrease osteoclastogenesis and bone turnover [127]. Monoclonal antibody against sclerostin augments Wnt-signaling-related osteoblast formation and inhibits bone resorption. Romosozumab treatment has been proved to maintain bone mass along with the increasing serum PINP level [128]. The application of romosozumab decreases the risk of fracture at the same time [129, 130]. During the treatment, therapeutic window of treatment with neutralizing anti-SOST antibodies is expected to be considerably large because an increase in bone formation is associated with a slight decrease in bone resorption [87]. In the animal model with sclerostin gene mutation, the bone strength increased along with the bone volume, and there is still no notable disadvantage on bone quality[131].

Effect of Nutritional Vitamin D on Osteoporosis

As mentioned in the previous sections, vitamin D receptors exist on the osteoblast, osteoclast, osteocytes, and ECM in osseous tissue. Vitamin D defi-

ciency is predictive to low bone quality and quantity, and the pharmacologic concentration of active vitamin D would pose damage to osteoblast. Since nutritional vitamin D provides a microenvironment of physiologic concentration of 25(OH)D for bone tissue, we discussed the role of nutritional vitamin D in treating high and low bone turnover disorders. Serum concentration of 25(OH)D reflects the status of vitamin D. It has been noticed that body fat and body mass index influence the serum concentration of 25(OH)D because of the fat distribution and fat tissue around intestine[132]. When treating vitamin D deficiency, it has been noticed that there is no a linear correlation between the supplemented dosage of cholecalciferol and the response in the serum vitamin D [133]. Previous retrospective analysis of nondialysis-requiring CKD patients was conducted to assess the relative effectiveness of D2 versus D3 replacement on circulating 25(OH)D levels. The results showed cholecalciferol may be superior to ergocalciferol in treating nutritional vitamin D deficiency in nondialysis CKD [134]. The meta-analysis also indicates that vitamin D3 is more efficacious at raising serum 25(OH)D concentrations than is vitamin D2, and thus vitamin D3 could potentially become the preferred choice for supplementation [135]. It has been found that daily supplement of cholecalciferol with dosage of 1000 IU/day could cause the largest increment in the patients with more severe vitamin D deficiency(<10 ng/ml). The increment of 25(OH)2D would decrease if the starting value of 25(OH)D is higher. Single dosage supplement of cholecalciferol (such as 70,000 IU ~ 300,000 IU) had been applied in several clinical trials [136–138]. Such supplement provided a sustained increase in serum 25(OH)D for less than 2 months, and the incidence of adverse effect such as hypercalcemia were not common. Therefore, when treating the severe hypovitaminosis, monitoring the variation of serum 25(OH)D is important and supplement with higher dosage or intensive interval should be considered in more severe vitamin D deficient status [139].To date, the evidence of drug interaction and supplement of vitamin D, especially cholecalciferol is limited. As the previous sections mentioned, there was a huge margin in 25(OH)D concentration for vitamin D deficiency and the optimal concentration. Therefore, a daily dosage 1000 IU for children <1 year on enriched formula,1500 IU for breastfed children older than 6 months, 3000 IU for children >1 year of age, and around 8000 IU for young adults might be recommended for maintaining the bone health [83].

Conclusions

Bone tissue is composed of osteocytes, osteoblasts, and osteoclasts and tightly controlled by RANK/OPG system. The increased in RANK/RANKL ratio and decreased in OPG levels will accentuate the osteoclast-related bone resorption. Excessive of Wnt/β-catenin signaling inhibitors, including DKK1 and SOST also attenuate the osteoblast viability and increase osteoclast activity resulted in an obvious bone quantity reduction. Abnormality of bone turnover disorders deteriorates bone structural arrangement and decreases bone quality, which cause bone fragility and bone loss. High PTH level stimulated by phosphate burden and vitamin D deficiency affects RANKL and OPG activity in osteoblasts and sequentially activates osteoclast-related bone resorption. Vitamin D deficiency is associated with increased bone resorption, insufficient calcium–phosphate absorption, decreased osteoblast activity, and sequential loss in bone quantity. In high turnover bone disorders, adding nutritional vit-D on the anti-resorption agent will lessen the decreased bone resorption and increase the therapeutic window. Similarly, in osteoporosis patients with low bone turnover, adding nutritional vit-D on osteoanabolic agent therapy will further increase bone formation and produce more good quality bone. Therefore, adequate vitamin D concentration might be recommended for maintaining the bone health in CKD.

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