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REVIEW

Old and New Drugs for the Management of Bone Disorders in CKD

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Abstract

Disturbances in mineral and bone metabolism are common in patients with chronic kidney disease (CKD), especially those undergoing dialysis. Renal osteodystrophy, which describes an alteration of bone morphology, is an important component of this systemic disorder and may explain the elevated risk of fracture which adversely affects morbidity and mortality. The most common form of renal osteodystrophy is high-turnover bone disease (osteitis fibrosa), which is induced by secondary hyperparathyroidism (SHPT). During the past decade, there has been considerable advances in the management of SHPT, with the introduction of the calcimimetic agents, the optimized use of nutritional and active vitamin D, and the accumulated experience with surgical parathyroidectomy. Studies supported that these advances could translate into improvement of renal bone disease and fracture prevention, as well as decreasing the risk of cardiovascular events and mortality. In this review, we summarize the available clinical evidence on the effect of old and new drugs on bone disorders in patients with CKD.

Keywords Renal osteodystrophy · Secondary hyperparathyroidism · Vitamin D · Calcimimetics · Parathyroidectomy

Introduction

Disturbances in mineral metabolism and bone disease are common in patients with chronic kidney disease (CKD). Declines in kidney function lead to impaired phosphate excretion, positive phosphate balance, and elevated levels of fibroblast growth factor 23 (FGF23) [1]. The elevated FGF23 helps prevent hyperphosphatemia by stimulating urinary phosphate excretion, but it also suppresses biosynthesis of 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], leading to early development of secondary hyperparathyroidism (SHPT) [2, 3]. In advanced CKD, elevated serum phosphorus, decreased serum calcium, and skeletal resistance to PTH further contribute to increased synthesis of parathyroid hormone (PTH) and parathyroid cell proliferation. In the course of parathyroid hyperplasia, there is a progressive reduction in the expression of calcium-sensing receptor (CaSR) [4], vitamin D receptor (VDR) [5], and the Klotho-FGF receptor complex [6], which renders the parathyroid cells less responsive to extracellular calcium, 1,25$(OH)_2$D, and FGF23, respectively, leading to further progression of SHPT [7].

These disorders in mineral metabolism are known as CKD-mineral and bone disorder (CKD-MBD), defined by the Kidney Disease: Improving Global Outcomes (KDIGO) [8]. Renal osteodystrophy (ROD), which describes an alteration of bone morphology in patients with CKD, is one component of the systemic disorder of CKD-MBD and may explain the elevated risk of fracture in these patients. The types of ROD can be defined on the basis of turnover and mineralization as follows: mild, osteitis fibrosa (hyperparathyroid bone disease), osteomalacia (mineralization defect), adynamic (low-turnover bone), and mixed [9]. Among these, the most common form is osteitis fibrosa [10], which is characterized by excessive rates of bone resorption by osteoclasts in response to high levels of PTH. Osteoblastic bone formation is also activated, but the newly formed bone matrix is inadequately mineralized and does not sufficiently compensate for the lost bone mass, leading to progressive bone loss

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and increased bone fragility. Indeed, the Dialysis Outcomes and Practice Patterns Study (DOPPS) demonstrated that intact PTH levels above 900 pg/ml are associated with an elevated risk for fracture [11], although conflicting results have been reported in smaller studies [12]. Therefore, the main purpose of managing SHPT is, although not limited to, to improve bone disease and ultimately reduce the risk of fracture.

Over the past 15 years, there has been considerable advances in the management of SHPT, with the introduction of the calcimimetic agents [13], the optimized use of nutritional and active vitamin D, and the accumulated experience with surgical parathyroidectomy (PTx). In this review, we summarize the available clinical evidence on the effect of old and new drugs on bone disorders in patients with CKD.

Active Vitamin D

Vitamin D metabolism is progressively altered in CKD. Physiologically, cholecalciferol (D_3) [or ergocalciferol (D_2)] are first hydroxylized in the liver into 25-hydroxyvitamin D (25(OH)D; calcifediol) which is subsequently hydroxylized in the kidney into 1,25$(OH)_2$D (calcitriol) [14]. Calcitriol can then be regarded as a calcitropic steroid hormone facilitating calcium entry into the body and steering (suppressing) PTH secretion at the parathyroid gland.

In advancing CKD, it was long believed that the pure reduction in kidney mass limits the renal capacity to activate 25(OH)D, but now it is known that increasing serum levels of FGF23 powerfully inhibit renal 1α-hydroxylase activity leading to early and direct suppression of calcitriol synthesis independent of kidney mass [15]. Consequently, transient or sustained hypocalcemia and SHPT may develop.

Therefore, calcitriol or other active vitamin D analogues (alfacalcidol, doxercalciferol, paricalcitol, maxacalcitol etc.) were the mainstay of SHPT management in progressive and end-stage CKD for decades. However, over the last 20 years evidence accumulated that treatment indications must be carefully chosen due to the potential risk of hypercalcemia, extraosseous (especially cardiovascular) calcification and PTH oversuppression associated with the use active vitamin D compounds [16]. Furthermore, the stage of CKD, and SHPT, in which to start active vitamin D therapy are not clearly defined, since moderate elevations of PTH in stages G3a–G4 are probably adaptive in order to overcome bone resistance to PTH and to facilitate phosphate excretion. Accordingly, the KDIGO CKD-MBD guideline update 2017 stated that the "optimal PTH levels are not known" in CKD patients not on dialysis, advised to correct hypocalcemia, hyperphosphatemia and vitamin D deficiency if present, and consider more trends of increasing PTH levels than absolute levels [17].

Data from the Paricalcitol Capsule Benefits in Renal Failure–Induced Cardiac Morbidity (PRIMO) and Oral Paricalcitol in Stage 3–5 Chronic Kidney Disease (OPERA) trials caused additional caution with regard to the use of active vitamin D analogues in patients in CKD stages G3a–G4 [18, 19]. These two studies were designed to address the question, if paricalcitol could potentially regress or slow the progression of left ventricular hypertrophy in appropriate patient cohorts. This hypothesis was well based on preclinical, biological, and clinical pilot data linking VDRs in the myocardium with re-modeling via the local renin-angiotensin-system [20, 21]. However, over 1-year follow-up periods, no such cardiac benefits could be observed in these randomized controlled trials compared to placebo, while in both studies hypercalcemia occurred quite frequently (23% in PRIMO, 43% in OPERA) in the paricalcitol group and also trends in hyperphosphatemia development were seen versus placebo. Here, and based on these studies, the current KDIGO guideline now states that "calcitriol and vitamin D analogues not be routinely used" in CKD patients not on dialysis, and that it is reasonable to reserve their use "for patients with CKD G4–G5 with severe and progressive hyperparathyroidism" [17]. This change was perceived as quite a paradigm shift compared to past recommendations, but possibly also as a necessary step given the new knowledge of the active vitamin D associated adverse effects (increases in FGF23, progression of vascular calcification etc.).

In dialysis patients (CKD stage G5D), current recommendations are however different, and active vitamin D analogues are considered important in controlling and preventing autonomous progression of SHPT. The KDIGO guideline suggests that "calcimimetics, calcitriol, or vitamin D analogues, or a combination of calcimimetics with calcitriol or vitamin D analogues" can be administered in case PTH-lowering therapies are required, without imposing a hierarchy between these two groups of compounds [17]. Pragmatically, the presence of low calcium levels and well controlled phosphatemia would favor the use of active vitamin D analogues in dialysis patients, while hyperphosphatemia and calcium levels at the higher end would tip the scale towards calcimimetics.

The effects of calcitriol and active vitamin D compounds on bone turnover in CKD patients are quite strongly connected to their effects on PTH levels. More than three decades ago, Baker et al. showed that calcitriol protected against the development of histological evidence of osteitis fibrosa, but not of osteomalacia, in a bone biopsy-guided study of 76 hemodialysis patients [22]. In this instance, insufficient PTH lowering keeps an elevated bone turnover going, however, oversuppression leads to low turnover, the so-called adynamic bone. The latter seems associated with increased extraosseous calcification

and calciphylaxis, thus creates a risk scenario, especially in dialysis patients, and should be avoided [23, 24]. What makes it difficult is that there are no definite PTH thresholds that can be given in order to improve guidance on treatment decisions, and there may be substantial differences in PTH target levels among populations (e.g. Japanese vs. Caucasian patients) [17, 25].

Bone mineral density (BMD) data under calcitriol treatment are only available for kidney transplant recipients in their first year after transplantation. Here, calcitriol is well able to protect from glucocorticoid bone loss [26], but no concise comments can be given on its modifying effects on post-transplant CKD-MBD. Systematic analysis of fracture risk or fracture risk prevention, or of bone histomorphometry, under active vitamin D treatment is not available to date in any stage of CKD.

Nutritional Vitamin D

Data on the importance nutritional vitamin D in CKD are unfortunately limited. Traditionally, it had been considered that vitamin D supply may be inconsequential, because the key issue is calcitriol deficiency due to loss of renal function, and if this is therapeutically corrected by calcitriol (or active vitamin D analogue) replacement, no additional supplementation with vitamin D_3 (or D_2) is required. The latter had even been regarded as ineffective, because it was thought that substrate availability had no impact if 1-alpha-hydroxylation is blocked.

Meanwhile, paradigms shifted into two different and novel directions. First of all, data were generated that there is still some relationship between vitamin D status, calcitriol production, and PTH levels, respectively [27]. Second, autocrine or paracrine (inducible) 1α-hydroxylase activities in non-renal cells (lymphocytes, heart, bone etc.) may serve as targets and be responsible for the so-called pleiotropic effects of vitamin D [28].

Ravani et al. provided data on associations of vitamin D deficiency [low 25(OH)D levels] and impaired calcitriol availability with increased PTH serum levels in 168 CKD patients not on dialysis [27]. Their study further indicated a significant mortality risk in subjects with vitamin D deficiency. Stubbs et al. demonstrated in dialysis patients with vitamin D deficiency that high-dose vitamin D supplementation not only corrected 25(OH)D serum levels, but still also increased calcitriol levels, associated with an improved immune function of circulating monocytes [29]. However, at first glance data on high-dose nutritional vitamin D seem disappointing as an intervention to control SHPT development in CKD patients not on dialysis. Meta-analyses recently demonstrated significant rises of 25(OH)D levels under supplementation, but no changes in PTH serum concentrations [30]. No such change may however alternatively mean still some control, because a further PTH increase was prevented—therefore, these data would not essentially justify ruling out any benefit of nutritional vitamin D on SHPT progression in predialysis stages.

In advanced CKD, while observational studies quite strongly point to associations of vitamin D deficiency with impaired hard outcomes, there are no conclusive prospective data available on the relationship of vitamin D supplementation with outcomes including mortality, morbidity, fracture risk, BMD, bone biomarkers etc. In the absence of such data, the current KDIGO guideline therefore pragmatically decided to apply guidelines recommendations for the normal population to CKD patients [17]. Depending on the source of the guideline (Institute of Medicine or Endocrine Society), 25(OH)D serum levels of ≥ 20 or ≥ 30 ng/ml should thus be targeted [31, 32], and as such levels are frequently not even reached in the normal population, most CKD patients would require some kind of supplementation. On average, doses would vary between 600 and 2000 IU vitamin D_3 equivalent per day.

One key question is how to address vitamin D status in the management of SHPT in CKD patients not on dialysis. As outlined above, there are hardly any reliable interventional data on the impact of nutritional vitamin D on SHPT progression. Moe et al. found a PTH lowering effect of high-dose vitamin D_3 (4000 IU/day for 1 month, then 2000 IU/day) comparable to doxercalciferol in a short-term study over 3 months in CKD patients not on dialysis, but sustainability remained questionable [33]. A new player is this context may be extended-release calcifediol (ERC), which is already available for treatment in the US. ERC is an especially coated 25(OH)D preparation constantly releasing during intestinal passage over 12 h. This mode of action avoids serum peaks of 25(OH)D and pharmacodynamically seems to prevent from feedback loop interactions getting activated, i.e. catabolizing 24-hydroxylases do not get activated and 1α-hydroxylases stay active [34].

Strugnell et al. performed a pivotal placebo-controlled trial in patients in CKD stages G3a–G4 with elevated serum PTH levels demonstrating both significant increases of 25(OH)D and decreases of PTH serum concentrations by ERC treatment, with concomitant decreases in bone turnover biomarkers [35]. Concerning safety, no relevant changes in calcium and phosphate levels were observed. Of note, serum 25(OH)D levels of ≥ 50 ng/ml were needed to see substantial PTH lowering in this cohort, raising the question of how an adequate vitamin D status should become defined in CKD patients not on dialysis. Finally, another question remains: would it potentially be equally effective, if such 25(OH)D levels were reached by high-dose nutritional vitamin D administration, or does the

pharmacodynamic specificity of ERC make the difference? The latter issue is currently under investigation.

Calcimimetics

The CaSR was first identified in 1993 as a G protein-coupled receptor sensitive to calcium and other extracellular cations [36]. The principle physiological function of the CaSR is in the control of extracellular fluid calcium concentration, reflected by the location of the receptor in the parathyroid glands and in the renal tubules [36, 37] where it respectively modulates PTH secretion and renal tubular calcium handling. Thus, the CaSR plays a pivotal role in the regulation of calcium homeostasis, achieving very tight control of extracellular calcium within a narrow physiological range. The receptor is expressed in many other tissues including bone, gut, and brain [38]. Unsurprisingly, activating and inactivating mutations of the CaSR may be associated with profound disturbances of calcium metabolism and mineral ion homeostasis, whereas acquired disturbances of the CaSR may be associated with progressive hyperparathyroidism in patients with falling GFR, where failure of the vitamin D-endocrine system and retention of phosphate lead to decreased extracellular calcium and compensatory hyperparathyroidism mediated via the CaSR. Phosphate further augments the drive to hyperparathyroidism by direct actions on the parathyroid cells which increase PTH synthesis and proliferative activity in the parathyroid glands [39, 40]. Of note, recent work has shown that phosphate acts directly on the CaSR, and it thus appears likely that the stimulation of the parathyroids by hyperphosphatemia is mediated via an additional direct mechanism involving the CaSR [41].

The central role of the CaSR in the pathogenesis of SHPT points to the CaSR as an attractive therapeutic target. The rapid development of allosteric modulators of the CaSR, initially NPS 568 and later AMG 073 (cinacalcet), attests to the importance of this therapeutic target [42]. Cinacalcet was the first clinically usable calcimimetic agent and has been in increasingly widespread use since 1993 [13]. Predictably its actions are to lower simultaneously PTH secretion and serum calcium concentration, an action that requires that the drug significantly shifts the normal sigmoid relationship between calcium and PTH to the left [43]. Cinacalcet has proved extremely effective with sustained responses in these patients [44], although with a target receptor so widely expressed, it is not surprising that certain unwanted off-target effects have emerged. Fortunately, these have generally been mild.

A further development in the area of CaSR modulation comes from the development of etelcalcetide, a peptide agonist of the receptor [45]. This peptide, which is administered by intravenous injection, activates the CaSR powerfully, thereby resulting in actions similar to those of cinacalcet. A critical feature of etelcalcetide is its resistance to degradation in plasma—the elimination of etelcalcetide is almost entirely renal and although the half-life in the presence of normal GFR is short, it is greatly prolonged in ESRD. This prolongation enables intermittent intravenous administration of etelcalcetide after dialysis with sustained action on the parathyroids resulting. Placebo-controlled studies using etelcalcetide have attested to its efficacy [46], and so also have comparative studies with cinacalcet where etelcalcetide was seen to be at least as effective as cinacalcet, carrying also the benefits of good tolerability (though are no better than cinacalcet) and very high levels of patient adherence reflecting the parenteral route of administration [47].

The flip side of calcimimetic drug development has been attempts to identify agents that *reduce* the sensitivity of the CaSR to ambient calcium concentration, thereby stimulating the release of PTH. Calcilytics are small organic molecules that act as negative allosteric modulators and, like calcimimetics, bind the transmembrane domain of the receptor [48]. The main potential therapeutic area is osteoporosis where it had been hoped that intermittent doses of a calcilytic agent would serve to mimic the effects of intermittent exogenous administration of synthetic human PTH, a therapy of proven efficacy in the treatment of osteoporosis [49, 50]. In phase II clinical studies using calcilytic agents, several have been tested and all generated rapid increases of PTH lasting from 8 or 12 h. Unfortunately, accompanying changes in the levels of bone markers were generally small, and there was no discernible effect on bone density [42]. In one study using ronacaleret for osteoporosis in postmenopausal women, despite significant changes in bone markers, comparable to those in patients treated with teriparatide, only very small changes of bone density were seen in the ronacaleret-treated patients, in contrast to those receiving alendronate or teriparatide [51]. Theoretically, calcilytics might be considered as a therapeutic option for adynamic bone disease in CKD patients, but this possibility has not been fully explored.

The pivotal role of PTH in the regulation of bone metabolism, alongside the expression of the CaSR in bone, raises important questions as to the skeletal consequences of CaSR modulating agents (calcimimetic or calcilytics). Clearly, osseous effects of calcimimetic treatment could be direct, mediated via the CaSR in bone, or indirect mediated via calcium, phosphate, PTH, vitamin D or FGF23. The possibility

that the CaSR mediates anabolic input to the skeleton is supported by studies of Al-Dujaili et al. in transgenic animals null for CaSR on osteoblasts, but not parathyroid, who found that PTH exerted a reduced bone anabolic effect [52]. Díaz-Tocados et al. infused physiological doses of PTH in parathyroidectomized rats and found that the anabolic effect on bone was increased further by concomitant administration of a calcimimetic [53]. Potentially, this could be therapeutically useful by mitigating the loss of PTH-induced anabolic input in patients overtreated with active vitamin D and/or calcium.

While there is no doubt that calcimimetic agents (cinacalcet is the best evaluated) are capable of improving the metabolic profile of patients with CKD and SHPT, as well as those with primary hyperparathyroidism and autonomous hyperparathyroidism following renal transplantation, effects on bone are much less clear. Even more problematic is the matter of patient-level outcomes in relation to the skeleton, as well as in other tissues. Thus, a major focus has been on the effect of these agents on cardiovascular events, as well as parathyroid- and skeletal-related events of this type—parathyroidectomy/fracture are also very important.

Because over treatment with calcium and vitamin D compounds has been associated with the development of low-turnover (adynamic) bone disease, the possibility of a similar problem in relation to overzealous treatment with cinacalcet is relevant. In addition to the experimental studies discussed above, this has been approached by investigators looking at biochemical bone markers and also bone histology and fracture. Several small studies have been undertaken to examine this and will be described now. Malluche et al. [54] examined bone markers (bone-specific alkaline phosphatase—BSAP and N-telopeptide—NTx) in 32 dialysis patients with mild-to-moderate hyperparathyroidism. Both biochemical markers were elevated at baseline and fell in cinacalcet-treated patients while increasing further in placebo-treated patients over the one year period of observation. In the Bone Histomorphometry Assessment for Dialysis Patients with Secondary Hyperparathyroidism of End Stage Renal Disease (BONAFIDE) study, BSAP, NTx, osteocalcin, and tartrate resistant acid phosphatase (TRAP) were followed in 40 patients treated with cinacalcet [55]. The resorption markers (NTx and TRAP) decreased significantly from the elevated baseline levels, as did the bone formation marker, osteocalcin. BSAP did not change significantly.

More recently biochemical bone markers have been examined in etelcalcetide-treated patients. In a comparative study between cinacalcet and etelcalcetide, BSAP and C-terminal telopeptide both decreased following calcimimetic treatment, with effects on etelcalcetide slightly greater than those seen with cinacalcet [47]. Similar results were obtained by Shigematsu et al. with TRACP-5b levels decreasing in etelcalcetide-treated patients though with less change in BSAP—indeed, there was transient increase of BSAP followed by decrease in etelcalcetide-treated patients in the early phase after initiation [56].

Bone histology was examined by Malluche et al. in 19 cinacalcet-treated patients and compared with results from 13 receiving placebo [54]. Bone turnover was elevated in the majority at baseline. Cinacalcet treatment decreased PTH and also activation frequency, bone formation rate/bone surface, and fibrosis surface/bone surface. Three cinacalcet-treated patients developed adynamic bone disease (in two of these PTH was over suppressed to less than 100 pg/ml). These histomorphometric changes broadly correlated with the changes in BASP and NTx.

In the single-arm BONAFIDE study [55], 110 patients with PTH at least 300 pg/ml underwent a baseline biopsy and a further 77 underwent second bone biopsy after 6–12 months of cinacalcet treatment. Evidence of cinacalcet effect was seen by PTH reduction from 785 to 480 pg/ml with significant reductions of bone turnover parameters in most patients—mean rate/tissue area from 728 to 336 $\mu m^2/mm^2$/day, osteoblast perimeter/osteoid perimeter from 17.4 to 13.9%, and eroded perimeter/bone perimeter from 12.7 to 8.3%. No patient was defined by normal bone histology at baseline with 20 normal at 12 months. Only two patients developed adynamic bone disease, both with PTH under 150 pg/ml. Most patients at the end of the study had persisting mild hyperparathyroidism or mixed uremic osteodystrophy. Thus, when used in this way, the risk of the unintended induction of low turnover/adynamic bone disease by cinacalcet appears to be low. One can surmise that this potential benefit of PTH control using a calcimimetic, rather than a vitamin D compound, may be a CaSR mediated phenomenon [52].

The first evidence that cinacalcet might have a favorable effect on fracture rate in hemodialysis patients came from a post hoc analysis of data from four similarly designed randomized studies comprising a total of 1184 subjects [57]. Randomization to cinacalcet resulted in the anticipated biochemical responses, accompanied by substantial reduction of fracture risk (RR 0.46, 95% CI 0.22–0.95). Subsequently in the much larger Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial, fracture was part of a pre-specified secondary analysis in which the relative hazard for fracture after adjustment of baseline characteristics and multiple fractures, was less impressive at 0.83 (95% CI 0.72–0.98).

In fact, in the unadjusted comparison the difference in fracture rate just failed to reach statistical significance [58]. The overall reduction of fracture rate by cinacalcet appeared to be more pronounced in older patients. To date, no evidence exists to demonstrate an effect of etelcalcetide on fracture rates in hemodialysis patients, despite data from studies in CKD rats demonstrating better preservation of bone structure and strength in animals treated with etelcalcetide [59]. Further studies will be needed to elucidate the potential of etelcalcetide in relation to this important clinical outcome.

Evocalcet is a relatively new oral calcimimetic widely used in Japan from where most of the clinical data have emerged. Evocalcet appears similarly effective to cinacalcet in respect of biochemical control in patients with SHPT, with the apparent advantage of a higher level of gastrointestinal tolerability than cinacalcet [60]. These clinical observations are consistent with earlier studies showing a favorable profile on gastric emptying in rats and the interaction with CYPs in liver microsomes [61].

Mindful of the plethora of new compounds capable of modifying the CaSR (only three of them used in clinical practice so far), this field is likely to continue its advance [42]. Perhaps the most intriguing possibilities lie in the area of organ specific agents targeting the CaSR where mitigation of unwanted side effects and/or exploitation of localized functions of the CaSR would be exciting developments.

Parathyroidectomy

Despite the advances in the medications for treating SHPT, a subset of patients with severe SHPT do not respond to PTH-lowering therapy, potentially leading to the development of high-turnover bone disease. PTx is the definitive therapy for treating such uncontrolled SHPT. This procedure drastically lowers PTH levels and simultaneously lowers serum calcium, phosphorus, and FGF23 levels [62, 63].

The effect of PTx on bone histology has been evaluated only in a few studies, probably because of the practical difficulty of performing bone biopsy before and after PTx in the same patient. These studies demonstrated that osteoclast bone resorption was markedly suppressed immediately after PTx, and this effect persisted in the long term. By contrast, osteoblast bone formation was further increased after PTx, but this effect was transient and was followed by a subsequent gradual decline [64, 65]. These findings indicate that there is an uncoupling of bone formation and bone resorption in the early postsurgical period, which corresponds to the rapid uptake of calcium and phosphate by the skeleton following PTx (a condition known as hungry bone syndrome). In accordance with the increased bone formation and mineralization following PTx, observational studies have consistently reported increased bone mineral density (BMD) following PTx [66, 67]. Of note, recent clinical studies reported the utility of BMD testing to predict fracture risk in dialysis patients [68, 69]. Thus, the improvement in BMD after PTx may have important implications in terms of fracture prevention.

As clinical fractures are not a common event even in the dialysis population, with the incidence being several-fold lower than mortality rates [70], evaluating whether PTx reduces the risk of fracture in patients with severe SHPT requires a large sample size. Until date, this question was explored only in one epidemiological study by Rudser et al. [71] using the United States Renal Database System (USRDS). This study compared incidence rates of fractures among 5,918 patients who underwent PTx with 16,328 control patients who were matched by age, race, sex, year of dialysis initiation, primary cause of kidney failure, and the dosage of intravenous vitamin D. The investigators demonstrated that PTx was associated with a lower risk for hip fracture (HR 0.68; 95% CI, 0.54–0.86) and combined fracture (hip, vertebral, distal radius, or wrist fracture; HR 0.69; 95% CI, 0.57–0.83). Although this observational study could not infer causality, their findings, in combination with the reported increase in BMD after PTx, support the possibility that PTx may reduce the risk of fracture in patients with severe SHPT [72].

The major concern with PTx is extremely low PTH levels after surgery because this condition has been linked with adynamic bone disease. However, it is still unknown whether the extremely low level of PTH, as a result of therapeutic intervention, actually contributes to increased bone fragility. One study reported that intact PTH levels less than 195 pg/ml were associated with an increased risk of hip fracture [12], but similar relationships were not observed in the much larger DOPPS analysis [11]. Importantly, patients with low PTH levels often have multiple risk factors for fracture, including aging, diabetes, malnutrition, and cardiovascular comorbidities that potentially contribute to falls [73, 74]. Thus, the associations of low PTH with elevated fracture risk reported in few previous studies could be attributed to residual confounding and may not be explained by low-turnover bone disease per se. In this regard, it is worth noting that in the USRDS study by Rudser et al. the risk reduction for fracture was pronounced among those who underwent total PTx versus subtotal PTx [71], suggesting that more aggressive PTH reduction may provide benefit in terms of bone strength. Interestingly, one bone biopsy study reported an activation of 'minimodeling' long after total PTx, which

is characterized by enhanced de novo osteoid formation and mineral apposition without signs of previous bone resorption, suggesting that PTH is not indispensable for maintaining bone volume after PTx [65]. These observations support the potential benefit of PTx on bone metabolism and might argue against the current belief that low PTH should be avoided for maintaining bone strength. However, additional studies are needed to address this possibility.

Phosphate Binders

While management of hyperphosphatemia is mainly intended to prevent vascular calcification and reduce the risk of cardiovascular disease, abnormal phosphate metabolism has been historically linked to the development of SHPT and high-turnover bone disease [75]. As such, control of PTH levels and management of bone metabolism have long been the therapeutic objective of phosphate binder therapy.

In the 1970s and 1980s, aluminum-based binders were the mainstay of therapy for hyperphosphatemia. They are highly effective, but their use was largely abandoned because of systemic aluminum toxicity, manifested as encephalopathy, anemia, and bone disease characterized by mineralization defect and suppressed bone turnover [76, 77].

As an alternative to aluminum salts, calcium-based binders have been used for the treatment of hyperphosphatemia. They are effective and inexpensive, but their administration results in elevations in serum calcium levels, especially in combinations with active vitamin D. The elevated serum calcium can cause suppression of PTH, which, theoretically, could reduce bone turnover [75]. If so, calcium-based binders might be used to help improve high-turnover bone disease. However, no placebo-controlled trials have evaluated the effect of calcium-based binders on bone histology. In a randomized trial comparing sevelamer hydrochloride and calcium carbonate, there were no changes from baseline in bone histomorphometric parameters in patients receiving calcium carbonate [78]. However, almost all of these patients have already been treated with calcium carbonate at study enrollment, which limited the ability to examine the effect of starting calcium carbonate on bone histology. Several studies have also shown increased BMD with calcium-based binders compared to placebo [79, 80], which might suggest improved bone strength. However, these effects could be achieved at the expense of accelerated vascular calcification, so the current KDIGO guideline suggests restricting the dose of calcium-based binders regardless of underlying bone disease or the presence of vascular calcification [17].

Sevelamer hydrochloride is a calcium-free, resin-based phosphate binder. Since this binder can cause metabolic acidosis, sevelamer carbonate has become available in several countries. The major characteristic of sevelamer is that it does not cause calcium overload. Compared with calcium-based binders, the use of sevelamer has been associated with lower serum calcium levels and higher levels of PTH and bone turnover markers [81]. In line with this, previous studies have reported that sevelamer-treated patients showed increased bone formation rate compared with those receiving calcium-based binders [78, 82]. These results may suggest that sevelamer is preferable to calcium-based binders for patients with adynamic bone disease, but additional studies are required to address this possibility.

Lanthanum carbonate is another calcium-free binder that effectively lowers serum phosphorus levels. In the same as sevelamer, lanthanum treatment has been associated with lower serum calcium levels, higher PTH levels, and a tendency towards higher bone turnover compared with calcium-based binders [83–85]. Thus, it could be assumed, but not proved, that lanthanum is preferable for patients with low bone turnover. In light of the experience with aluminum-induced bone disease, there has been a concern regarding the long-term safety of lanthanum, particularly with regard to bone toxicity. Indeed, studies reported a progressive increase in the concentrations of lanthanum in bone up to three years [83–86]. However, these concentrations were still very low, and no patients have developed aluminum-like effects on bone so far in previous studies [83–86]. Furthermore, in a recent analysis of post-marketing observational study, lanthanum prescription was not associated with increased risk of fracture during the 5 years of follow-up [87]. These data suggest that lanthanum does not accumulate to clinically relevant levels in bone, but additional studies would be required to fully confirm the safety of this binder.

Conclusions

During the past decade, the introduction of calcimimetics, the optimized use of nutritional and active vitamin D, and the accumulated experience with PTx have expanded the treatment options for SHPT in patients with CKD. Our current knowledge on the effects of these interventions on bone disorders are summarized in Table 1. Studies supported that these advances could translate into improvement of renal bone disease and fracture prevention, as well as decreasing the risk of cardiovascular events and mortality. Nonetheless, patients with advanced CKD, especially those receiving dialysis, still have unacceptably high risk of fracture, which adversely impacts morbidity and mortality. Clearly,

Table 1 Therapeutic options for bone disease in CKD patients

Intervention	Mechanism of action	Skeletal effect	Drawbacks
Active vitamin D (calcitriol, alfacalcidol, doxercalciferol, paricalcitol, maxacalcitol)	Inhibits *PTH* gene transcription to decrease PTH production	Improves high-turnover bone disease; no data on fracture prevention	May induce hypercalcemia, vascular calcification, and adynamic bone disease
Nutritional vitamin D (cholecalciferol, ergocalciferol)	Increases 25(OH)D but not effective in decreasing PTH	Unknown	Requires adequate kidney function to generate active $1,25(OH)_2D$
Extended-release calcifediol	Increases both 25(OH)D and $1,25(OH)_2D$ and decreases PTH production	Unknown	Data are limited to non-dialysis-dependent CKD patients
Calcimimetics (cinacalcet, etelcalcetide, evocalcet)	Increases sensitivity of the CaSR to inhibit PTH secretion	Improves high-turnover bone disease and may reduce fracture risk	May induce hypocalcemia; higher cost
Parathyroidectomy	Surgical resection of hyperplastic parathyroid glands	Improves high-turnover bone disease and may reduce fracture risk	Surgical risk; induces hungry bone syndrome, requiring high doses of calcium and calcitriol
Phosphate binders (calcium, sevelamer, lanthanum)	Binds dietary phosphate to reduce intestinal phosphate absorption	Calcium may lead to low bone turnover compared with sevelamer or lanthanum	Calcium may cause hypercalcemia and promote vascular calcification compared with sevelamer or lanthanum

$1,25(OH)_2D$: 1,25-dihydroxyvitamin D, 25(OH)D: 25-hydroxyvitamin D, *CaSR* calcium-sensing receptor, *PTH* parathyroid hormone

additional studies are needed to establish the optimal treatment of CKD-MBD for preventing fractures and other adverse clinical outcomes.

Compliance with Ethical Standards

Conflict of Interest Hirotaka Komaba has received honoraria, consulting fees, and/or grant support from Bayer Yakuhin, Chugai Pharmaceutical, Japan Tobacco, Kyowa Kirin, Novartis, and Ono Pharmaceutical. Markus Ketteler has received honoraria for consulting and lecture fees from Amgen, Bayer, Kyowa Kirin, Medice, Ono Pharmaceutical, Sanofi, and Vifor Pharma. John Cunningham has receive honoraria, consulting fees, and/or grant support from Vifor Pharma, Amgen, Merck, and Opko Pharma. Masafumi Fukagawa has received honoraria, consulting fees, and/or grant support from Bayer Yakuhin, Fresenius Kabi, Kissei Pharmaceutical, Kyowa Kirin, Ono Pharmaceutical, and Torii Pharmaceutical.

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