Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)

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Abstract

Disturbances in mineral and bone metabolism play a critical role in the pathogenesis of cardiovascular complications in patients with chronic kidney disease (CKD). The term “renal osteodystrophy” has recently been replaced with “CKD-mineral and bone disorder (CKD-MBD)”, which includes vascular calcification as well as bone abnormalities. Following this paradigm shift, the Japanese Society for Dialysis Therapy released guidelines for the management of secondary hyperparathyroidism in chronic dialysis patients, which prioritized improvement in survival, but not in bone abnormalities. According to these guidelines, parathyroid intervention, such as parathyroidectomy and percutaneous ethanol injection therapy, should be indicated if mineral disorders cannot be managed by pharmacological means. Recently, several novel therapeutic tools, including sevelamer hydrochloride, calcitriol analogs, and cinacalcet hydrochloride have been introduced in the clinical setting in Japan. Harmonizing these therapeutic modalities, we should expect more effective management of CKD-MBD, leading to the improvement of morbidity and mortality in this patient population.

Key words: chronic kidney disease-mineral and bone disorder, cinacalcet hydrochloride, JSDT guidelines, secondary hyperparathyroidism, calcitriol analog

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Introduction

The kidney plays a leading role in maintaining calcium and phosphorus homeostasis in collaboration with other organs, i.e., the parathyroid gland, intestines, and bones. It is not only the target organ for various hormones, such as parathyroid hormone (PTH), but also the principal site for the production of calcitriol (1,25-dihydroxyvitamin D). Thus, along with the progression of chronic kidney disease (CKD), various abnormalities of mineral and bone metabolism develop, which can result in significant consequences (1). Traditionally, such disorders have been considered with regard to the bone lesion itself, but it has become increasingly evident that mineral and bone disorders have a critical role in the pathogenesis of extraskeletal calcification including the vasculature, thereby resulting in cardiovascular complications and mortality. Thus, in place of the term ‘renal osteodystrophy (ROD)’, a new term, ‘CKD-mineral and bone disorders (CKD-MBD)’ has recently been proposed to describe this broad clinical syndrome that develops as a systemic disorder (Fig. 1) (2). Following this paradigm shift, the Japanese Society for Dialysis Therapy (JSDT) released the Guidelines for the Management of Secondary Hyperparathyroidism in Chronic Dialysis Patients, which prioritized improvement in survival, but not in bone abnormalities (3, 4). Here, we review the current strategies for the treatment of CKD-MBD.

Target Levels for Serum Phosphorus, Calcium, and PTH

Current clinical guidelines, such as the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines, recommend that serum levels of calcium and phosphorus should be maintained within the target range to avoid the development of vascular calcification (5). The focus of these guidelines was to regard mineral and bone disorders as systemic...
Among the risk factors related to vascular calcification, hyperphosphatemia is evidently the major contributing factor. It is well known that vascular calcification is not a simple process of passive mineralization, but also includes several mechanisms similar to bone formation that are exemplified by upregulation of osteochondrogenic differentiation markers (10-12). Phosphate retention also stimulates PTH secretion and induces parathyroid hyperplasia either directly or indirectly (13, 14). In addition, higher serum phosphorus and calcium-phosphorus product levels are associated with the progression of CKD (15). Thus, there is every reason to control the serum phosphorus levels in patients with CKD.

Dietary phosphorus restriction and conventional dialysis alone are usually ineffective in controlling hyperphosphatemia, hence, most dialysis patients require phosphorus binders. Aluminum-based binders were once used extensively, but were abandoned when aluminum was found to contribute to anemia, myopathies, dementia, and low-turnover bone disease (16). Since then, calcium-based binders have predominantly been in use, but they have been linked to arterial calcification observed in hemodialysis patients (17). Recently, non-calcium and non-aluminum-based binders such as sevelamer hydrochloride have been introduced in clinical practice in Japan. Several studies have suggested that excessive calcium intake may worsen vascular calcification (17), and that the progression of coronary vascular calcification was slower in patients on sevelamer, than in those on calcium-based phosphorus binders (18, 19); therefore, the K/DOQI guidelines restricted the total dose of calcium carbonate to 3,750 mg/day, and recommended the use of sevelamer, especially for patients with hypercalcemia (5). In the JSDT guidelines, the total dose of calcium carbonate was restricted to 3,000 mg/day, in consideration of the body size of Japanese patients (3, 4).

Despite the possible beneficial effects of sevelamer on the progression of vascular calcification, it is unknown whether the choice of a phosphorus binder is likely to improve the survival outcome of dialysis patients. It has recently been shown that the use of calcium-based binders in an incident dialysis population was associated with a significantly higher mortality rate when compared to sevelamer (20). By contrast, the Dialysis Clinical Outcomes Revisited study failed to demonstrate a significant reduction in mortality in patients treated with sevelamer compared to those receiving calcium-based phosphorus binders, except for individuals over 65 years of age (21). Therefore, the use of sevelamer should be considered on a case-by-case basis, until further well-designed studies clearly show its superiority over the calcium-based phosphorus binder. Given that many Japanese patients suffer from adverse events such as severe constipation, combination treatment with sevelamer and calcium carbonate may be effective and tolerable (22).

A new salt form of sevelamer carbonate has recently been developed and is in the experimental stage (23). This new agent seems to be especially useful in patients with CKD who are not yet receiving hemodialysis, because it does not induce hyperchloremic acidosis. It is also promising for current hemodialysis patients, as it eliminates the need for...
monitoring of metabolic acidosis.

Lanthanum carbonate is an alternative effective phosphorus binder that can facilitate phosphorus control while limiting calcium intake (24). Despite the possibility of metal accumulation in tissues over time like aluminum-based binders, there is no evidence from preclinical studies that lanthanum can cross blood-tissue barriers including the blood-brain barrier. A two-year comparative study of lanthanum carbonate versus standard therapy, demonstrated that lanthanum carbonate is effective and does not adversely affect cognitive function compared to the standard therapy (25). Lanthanum carbonate was also highly effective in Japanese dialysis patients (26). However, it should be noted here that the increase in lanthanum carbonate concentration in the liver, lung, and kidney has been reported in an animal model of renal failure (27), although this finding has been challenged as a contamination artifact (28). Further clinical studies are required to establish the long-term safety of lanthanum regarding tissue deposition, and its efficacy on vascular calcification and mortality.

Management of Secondary Hyperparathyroidism

Treatment of secondary hyperparathyroidism is the cornerstone in the management of CKD-MBD. It is well established that phosphorus retention and calcitriol deficiency play critical roles in the pathogenesis of secondary hyperparathyroidism (29). Recent clinical studies revealed that fibroblast growth factor 23, a newly identified phosphaturic factor, is progressively elevated to prevent hyperphosphatemia in CKD, at the expense of low calcitriol and hyperparathyroidism (30, 31). Thus, rigorous control of serum phosphorus levels and administration of calcitriol or its analogs are the mainstream treatment for secondary hyperparathyroidism (5).

Before initiating treatment for secondary hyperparathyroidism, clinicians should recall the JSDT guidelines, which state that normalization of serum phosphorus and calcium concentrations is a prerequisite for PTH control (3, 4). Calcitriol has been shown to suppress PTH secretion effectively and inhibit cell proliferation in parathyroid hyperplasia (32, 33), but this treatment may increase the risk for hypercalcemia and hyperphosphatemia, resulting in withdrawal or a reduction in the dose of calcitriol. To overcome these problems, new calcitriol analogs with less calcemic action than calcitriol, such as paricalcitol (34), doxercalciferol (35), maxacalcitol (36), and falecalcitriol (37) have been developed. Among these, maxacalcitol and falecalcitriol are now commercially available in Japan. However, even maxacalcitol treatment readily induces hypercalcemia in patients with advanced hyperparathyroidism, and parathyroid interventions such as parathyroidectomy are often required (38). Thus, identifying a patient with refractory hyperparathyroidism is a major problem.

Recently, pathophysiological aspects of parathyroid hyperplasia have been extensively elucidated (39, 40). In the initial stage of CKD, several mitogenic stimuli, such as phosphorus load and reduced production of calcitriol, induce hyperparathyroidism and proliferation of parathyroid cells (diffuse hyperplasia). Some cells in the parathyroid with diffuse hyperplasia, especially those exhibiting reduction of vitamin D receptor (VDR) and calcium-sensing receptor (CaSR), proliferate vigorously and become encapsulated (nodular hyperplasia). It has been well recognized that cells in nodular hyperplasia have reduced numbers of VDR and CaSR, thus usually refractory to medical therapies (41, 42). Development of nodular hyperplasia has been most efficiently diagnosed by ultrasonography, and 0.5 cm’ or 1 cm in diameter has been considered to be the critical size (43). Hence, dialysis patients with severe hyperparathyroidism and such large parathyroid gland(s) should undergo parathyroid intervention if they do not respond to a short course of medical intervention (Fig. 2) (44).

Parathyroid intervention

Parathyroid intervention, i.e., surgical parathyroidectomy and direct injection therapy, should be indicated for refractory hyperparathyroidism associated with nodular hyperplasia. There are three surgical approaches: total parathyroidectomy with or without autotransplantation, subtotal parathyroidectomy, and minimally invasive surgery (45, 46). In general, total parathyroidectomy with forearm autograft is preferred for secondary hyperparathyroidism, especially in patients who require long-term hemodialysis, because a recurrent, enlarged autograft can easily be removed from the forearm (45). Minimally invasive surgery may be effective and less invasive in patients with one solitary radioactive nodule (46). Direct injection therapies, such as percutaneous ethanol injection therapy (PEIT), percutaneous calcitriol injection therapy (PCIT), and percutaneous maxacalcitol injection therapy (PMIT) are also effective treatments for refractory hyperparathyroidism (47-50). The main difference between parathyroidectomy and direct injection therapy is the selection of the target glands. In total parathyroidectomy with autograft, all glands are surgically removed and fragments from the smallest gland are transplanted in the forearm. In direct injection therapy, an enlarged gland with nodular hyperplasia is selectively infiltrated by ethanol or calcitriol (analogs), and other glands with diffuse hyperplasia are treated with medical therapy. The appropriate dose of calcitriol or its analogs must be used soon after direct injection therapy (51). In a recent clinical study, patients with one hyperplastic gland responded well to PEIT with respect to efficacy rate, remission period, and risk of relapse (52). As recommended by the JSDT guidelines, a patient with one enlarged gland is the best indication for PEIT (3, 4). The selection of the optimal method for parathyroid intervention should be determined by the number and location of enlarged glands, as well as the presence of ectopic glands.
Progression of parathyroid hyperplasia and current management strategy. Parathyroid glands exhibiting nodular hyperplasia are usually resistant to medical therapy, such as calcitriol or its analogs. Surgical parathyroidectomy or direct injection therapy is recommended for nodular hyperplasia. Calcimimetic agents are promising therapeutic tools, but it remains to be elucidated whether or not they can effectively regress the hyperplastic parathyroid glands.

Calcimimetic agents
Calcimimetic agents, such as cinacalcet hydrochloride, have been developed for the control of hyperparathyroidism in patients with CKD. These agents enhance the sensitivity of the parathyroid calcium-sensing receptors, thereby reducing levels of PTH, serum calcium and phosphorus, and calcium-phosphorus product (53). Cinacalcet therapy is also favorable to meet the practice guidelines. The combined data from three large randomized, placebo-controlled studies showed that treatment with cinacalcet in combination with conventional therapy, led to better achievement of the K/DOQI recommended target ranges (54). In Japan, a recent clinical study showed the efficacy and safety of cinacalcet therapy, even in patients with a longer average dialysis vintage (55). A post hoc analysis of the combined data from four similarly designed clinical trials showed that cinacalcet treatment significantly decreased the risks of parathyroidectomy, fracture, and cardiovascular hospitalization (56). It remains, however, to be elucidated whether or not calcimimetics can effectively control hyperparathyroidism in patients with nodular hyperplasia (57). Moreover, the economic impact of these expensive agents should be considered, especially in comparison with parathyroidectomy (58). Further investigation is required to elucidate these issues and establish the clinical significance of cinacalcet therapy in patients with CKD.

Possible Beneficial Effect of Vitamin D Therapy on Survival
Several clinical data uncovered CKD as a risk factor for vitamin D deficiency and current recommendations from K/DOQI emphasize the need to correct this deficiency by administration of a vitamin D preparation such as ergocalciferol. As 1-hydroxylase activity is impaired in CKD, activated vitamin D offers theoretical advantages and has been prescribed to dialysis patients. Recently, a retrospective analysis of hemodialysis patients reported that the mortality was lower among those treated with paricalcitol, a selective activator of VDR, compared to calcitriol (59). Since then, several investigators have speculated that calcitriol or its analogs may reduce cardiovascular morbidity and mortality in patients with CKD, especially dialysis patients. The mechanism of such an effect is not known, but one hypothesis suggests that calcitriol may have non-classical direct effects on the cardiovascular system (60). However, the effect of correction of calcitriol deficiency on cardiovascular mortality is not evident due to the retrospective nature of previous studies and the potential for confounding by unknown factors. Indeed, a recent systematic review and meta-analysis revealed that the evidence does not support the widespread use of calcitriol (analogs) in treatment of CKD (61). By contrast, a recent prospective analysis of case-control data indicated that incident dialysis patients who received paricalcitol had a significant survival benefit during the first 90 days of dialysis, compared with those who did not receive calcitriol or its analogs (62). Further detailed studies are required to validate the beneficial effect of selective VDR activators in CKD patients.

Conclusions
Disturbance in mineral and bone metabolism is one of the most important causes of increased cardiovascular mortality in CKD. According to recent clinical guidelines, including those released by the JSDT, the control of parathyroid function in CKD patients should be achieved without the risk of
vascular calcification. If mineral and bone abnormalities cannot be controlled with medical treatment, parathyroid intervention should be indicated to avoid prolonged and even potentially harmful medical therapy. Novel therapeutic tools, such as sevelamer hydrochloride, calcitriol analogs, and cinacalcet hydrochloride, have been introduced in the clinical setting. These new agents are promising, but further clinical research is required to harmonize these therapeutic modalities and to amend the current clinical guidelines.

References

35. Tan AU Jr, Levine BS, Mazess RB, Kyllo DM, Bishop CW, Knut-


