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Review Article

Management of chronic kidney disease–mineral and bone disorder: Korean working group recommendations

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Abstract

For Korean dialysis patients, chronic kidney disease–mineral bone disorder is a serious burden because of cardiovascular calcification and mortality. However, recent epidemiologic data have demonstrated that many patients undergoing maintenance hemodialysis are out of the target ranges of serum calcium, phosphorus, and intact parathyroid hormone. Thus, we felt the necessity for the development of practical recommendations to treat abnormal serum phosphorus, calcium, and iPTH in dialysis patients. In this paper, we briefly comment on the measurement of serum calcium, phosphorus, iPTH, dialysate calcium concentration, dietary phosphorus restriction, use of phosphate binders, and medical and surgical options to correct secondary hyperparathyroidism. In particular, for the optimal management of secondary hyperparathyroidism, we suggest a simplified medication adjustment according to certain ranges of serum phosphorus and calcium. Large-scale, well-designed clinical studies are required to support our strategies to control chronic kidney disease–mineral bone disorder in this country. Based on such data, our practice guidelines could be established and better long-term outcomes should be anticipated in our dialysis patients.

Introduction

Chronic kidney disease–mineral bone disorder (CKD-MBD) is a common complication occurring in CKD patients. In addition to hypercalcemia and hyperphosphatemia, CKD-MBD can cause vascular calcification and cardiovascular diseases (CVD), and these conditions are closely associated with an increased mortality rate. Recently, these associations have been demonstrated, even in early-stage CKD patients [1–3]. According to the end-stage renal disease registry of the Korean Society of Nephrology, there were 48,531 hemodialysis (HD) and 7,552 peritoneal dialysis (PD) patients in Korea in 2012, and CVD was the most common cause of death in dialysis patients [4].

We previously analyzed the serum levels of calcium (Ca), phosphorus (P), and intact parathyroid hormone (iPTH) from a total of 1,018 patients undergoing chronic HD in 17 centers throughout Korea [5]. The mean serum levels of Ca, P, and the Ca-P product were 9.1 mg/dL, 5.3 mg/dL and 48.0 mg^2/dL^2, respectively. When classified by the recommended range according to the Kidney Disease Outcome Quality Initiative

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(KDOQI) guidelines, about one half of the patients had uncontrolled hyperphosphatemia > 5.5 mg/dL. In addition, 270 patients (26.5%) had iPTH > 300 pg/mL whereas 435 patients (42.7%) showed iPTH < 150 pg/mL. This study demonstrated the current status of CKD-MBD in our HD patients, revealing that a relatively modest proportion of patients had values outside of the target range [5]. Those patients who were out of the target range might be associated with poor prognosis, including mortality secondary to CVD. Therefore, successful implementation of treatment guidelines is required with respect to CKD-MBD.

To improve the quality of care in CKD-MBD, global and regional guidelines were established and suggested target ranges and treatment protocols. In Korea, the KDOQI and the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines are well known and commonly used [6,7]. In both global guidelines, however, the level of recommendations is low because of scarcity of randomized controlled clinical trials. On regional bases, guidelines were published from Japan (Japanese Society for Dialysis Therapy, JSDT), Australia (the Caring for Australians with Renal Impairment, CARI), Great Britain (United Kingdom Renal Association, UKRA), and Europe (European Renal Best Practice, ERBP) [8–11]. The target levels of Ca, P, and iPTH presented in the aforementioned guidelines are summarized in Table 1.

The target ranges in these guidelines are not consistent, and we may have to choose one of them because we have no well performed epidemiological data showing associations between serum mineral values and patient outcomes in our dialysis population. Furthermore, in Korea, it is practically difficult to just adapt foreign guidelines because our treatment strategies are guided by the National Health Insurance Service (NHIS) standards. With regard to this point, we reviewed the CKD-MBD guidelines from different countries and suggest that our treatment recommendations to be applied in real practices of CKD-MBD in Korea.

Measurement of serum Ca, P, and iPTH

In dialysis patients, it is important to maintain serum Ca, P, and iPTH within the appropriate ranges. For this, serum Ca and P should be measured monthly or more frequently (depending on the clinical settings). The measurement of iPTH should be conducted at least once every 3 months.

Control of hyperphosphatemia and maintenance of serum Ca, P, and iPTH levels within the target ranges in CKD patients are the mainstay of the management of CKD-MBD. Thus, biochemical tests for Ca, P, and iPTH must be performed regularly, and it is recommended to measure patients' serum Ca and P at least once per month. The measurement interval of iPTH is 3–6 months by the KDIGO guidelines, and is 3 months according to the KDOQI and JSDT guidelines. Considering these three guidelines and our NHIS, we recommend that the iPTH level should be measured once every 3 months. However, laboratory tests may be performed more frequently based on clinical decisions until the test results are optimalized. In particular, biochemical tests should be performed more frequently during active suppression of secondary hyperparathyroidism using vitamin D receptor activators (VDRAs) or calcimimetics. Even when the value of each biochemical test result falls within the target range, it is important to identify a trend of change. If the iPTH levels are increased, serum alkaline phosphatase may also be measured, as necessary. In cases of decreased serum Ca level, the serum albumin concentration should also be measured to obtain the corrected Ca because only the total, but not ionized (biologically active), serum Ca concentration may be lowered by hypoalbuminemia. The corrected Ca concentrations can be calculated by two different formulae recommended by the KDIGO and JSDT guidelines.

KDIGO method [7]:
Corrected total Ca (mg/dL) = measured Ca (mg/dL) + 0.8 × [4 – serum albumin (g/dL)].
JSDT method [9]:
Corrected total Ca (mg/dL) = measured Ca (mg/dL) + [4 – serum albumin (g/dL)].

Table 2 summarizes our recommendation on the frequency of serum mineral measurements and their target ranges. In the latter part of this article, we will describe in detail the target ranges of serum Ca, P, and iPTH.

Consideration of dialysate Ca concentration

Although dialysate Ca concentrations may be individualized for successful HD, the KDIGO [7], ERBP [11], and JSDT [9] guidelines recommend that the dialysate Ca concentration be maintained between 2.5 mEq/L and 3.0 mEq/L (1.25–1.5mM). Serum Ca levels usually change in parallel with dialysate Ca

Table 2. Recommended measurement frequency and ranges of serum calcium, phosphorus, and parathyroid hormone in chronic kidney disease stage 5D

Serum parameters	Measurement frequency	Recommended range
Calcium	Once per mo	8.4–9.6 mg/dL
Phosphorus	Once per mo	2.4–5.0 mg/dL
Parathyroid hormone	Once every 3 mo	100–300 pg/mL

Table 1. Target levels of serum phosphorus, calcium, and parathyroid hormone presented by different guidelines

	Phosphorus (mg/dL)	Calcium (mg/dL)	Intact parathyroid hormone (pg/mL)
KDIGO [7]	Towards normal range	Towards normal range	2–9 × normal range
ERBP [11]	2.4–4.5	Towards normal range	100–800
UKRA [10]	2.78–4.64	8.8–10.0	Not mentioned
CARI [8]	~4.95	8.5–10.5	100–470
KDOQI [6]	3.5–5.5	8.4–9.5	150–300
JSDT [9]	3.5–6.0	8.4–10.0	60–240

CARI, Caring for Australians with Renal Impairment; ERBP, European Renal Best Practice; JSDT, Japanese Society for Dialysis Therapy; KDIGO, Kidney Disease: Improving Global Outcomes; KDOQI, Kidney Disease Outcome Quality Initiative; UKRA, United Kingdom Renal Association.

concentrations. Thus, a dialysate Ca concentration at 2.5 mEq/L lowers the serum Ca level, enabling the liberal use of VDRAs or Ca-containing phosphate binders. However, low dialysate Ca concentrations may provoke hypotension during HD [12–14]. In case of using cinacalcet, a higher dialysate Ca concentration may be advantageous to avoid hypocalcemia. Here, we recommend that the dialysate Ca concentration should be properly determined within the range of 2.5–3.0 mEq/L (1.25–1.5mM), considering the individual dietary intake of Ca and use of phosphate binders, VDRAs, and cinacalcet.

Dietary P restriction

In adult dialysis patients with serum P $>$ 4.5 mg/dL, the daily dietary P intake should be limited to $<$ 800 mg. To achieve the goal of limiting P intake while maintaining the protein intake, it is recommended that patients select diets with a low phosphorus–protein (P-P) ratio. Thus, P additives found in some carbonated beverages and processed meat should be avoided.

The current HD procedures and phosphate binders offer only limited effects of P removal, and it is necessary to restrict the dietary intake of P. The daily P intake of a healthy person is known to be approximately 1,000–2,000 mg [15], and it needs to be restricted to approximately 800 mg in adult dialysis patients [16]. An observational study reported that a higher dietary P intake and a higher dietary P-P ratio were associated with an increased mortality [17]. Consequently, dietary P intake restriction should be enforced for dialysis patients with serum P concentrations $>$ 4.5 mg/dL.

Organic P, which is ingested from food, can be categorized into vegetable and animal P, whereas inorganic P exists as an additive in processed foods [18]. P contained in vegetable-based foods, such as nuts, exhibits a low gastrointestinal absorption rate (bioavailability, 20–40%), while P contained in animal-based foods, such as yogurt, demonstrates a high gastrointestinal absorption rate (bioavailability, 40–60%). In particular, the bioavailability of inorganic P included as an additive and preservative in carbonated beverages reaches 80–100%. Thus, for the control of serum P concentrations, it is necessary to limit the intake of inorganic P and natural P contained in foods rich in animal protein. However, as the protein intake is also related to patient survival, it should be noted that the daily protein intake needs to be at least 1.1 g/kg [19]. If the serum P concentration is $<$ 2.4 mg/dL, the nutritional status of the patient should be re-evaluated, and the dietary intake of P and protein should be encouraged.

In general, the dietary P content is proportional to protein intake, as shown in the equation below [20].

$$\text{Dietary P (mg)} = 78 + 11.8 \times \text{protein intake (g)}$$

Thus, it is possible that restrictions on the dietary P intake can, in turn, lead to protein deficiency, as limiting dietary P intake is accompanied by a decrease in protein intake [21]. Furthermore, a previous study showed that dietary prescriptions of limited P intake did not increase the survival rate of dialysis patients [22]. It is not clear whether dietary treatments actually produce long-term benefits in improving hyperphosphatemia [23].

As shown in Table 3, there are large differences in the P-P ratio, depending on the food sources. Hence, if food with a low P-P ratio is selected, the goal of dietary P intake restriction may be achieved with maintaining protein intake. Because it is important to avoid the P additives included in carbonated beverages and processed meats, patients must avoid fast foods. In cases of cooking foods with a high P content, boiling the food is helpful for lowering its P content [16].

Table 3. Phosphorus and protein content of selected foods

Food	Common measure (g)	Phosphorus content (mg)	Protein content (g)	Phosphorus (mg) / protein (g) ratio
Chicken, leg, meat only, fried or fired	60	115.8	17.0	4.1
Chicken, breast, meat only, fried	60	148.8	20.0	4.5
Pork, ribs, roasted	60	135.6	14.0	5.8
Pork, belly	60	79.2	10.3	4.6
Beef, Korean cattle, loin	60	99.0	12.6	4.7
Beef, imported cattle, brisket, braised	60	112.2	14.0	4.8
Mackerel, broiled	60	144.0	14.5	6.0
Spanish mackerel, broiled	60	156.0	14.2	6.6
Chum salmon, smoked	60	141.0	13.8	6.1
Chicken's egg, broiled	60	123.6	7.3	10.2
Soybean curd, pressed	80	72.0	6.7	8.6
Potatoes, steamed	100	35.0	1.9	18.4
Sweet potatoes, steamed	100	40.0	1.1	36.4
Chestnuts, raw	60	40.8	1.9	12.8
Peanuts, dried	10	39.8	2.5	1.6
Milk, ordinary liquid milk	200	178.0	6.4	55.6
Yogurt, liquid type	150	93.0	2.3	62.0

Adapted with permission from the Nutritious Food Table, 8th Revision, 2011, National Academy of Agricultural Science.

Treatment of hyperphosphatemia

We suggest that serum P concentration be maintained within the target range of 2.4–5.0 mg/dL. In addition to adequate dialysis, the administration of phosphate binders is usually required to control hyperphosphatemia. The status of serum Ca and iPTH should be considered when selecting a phosphate binder.

It is well known that hyperphosphatemia in CKD patients stimulates PTH secretion from the parathyroid glands and induces soft tissue and vascular calcification [24,25]. In particular, the increased incidence of CVD in CKD patients has been known to be associated with abnormal Ca-P metabolism [26]. Consequently, maintaining the serum P level within the

normal range is vital for managing complications in these patients.

The target ranges of the serum P level differ modestly between the different guidelines. Determining the target range of the serum P was mainly based on the previous observational studies. Block et al [27] retrospectively studied 40,000 HD patients and reported that the relative risk of mortality was the lowest in patients who maintained their serum P concentrations within 3.5–5.5 mg/dL. Consequently, the KDOQI guideline set the target range at 3.5–5.5 mg/dL [6]. In 2009, the KDIGO guidelines recommended that serum P level be more strictly controlled by maintaining it within the normal range because of the lack of well-performed randomized controlled trials [7]. By contrast, a study from Japan reported that there was no difference in the mortality between patients who maintained serum P level within 3.6–5.0 mg/dL and those who maintained it within 4.1–6.0 mg/dL or 4.1–5.5 mg/dL [28]. As a result, the JSDT guidelines recommended that serum P level be maintained at 3.5–6.0 mg/dL [9]. In Korea, no longitudinal studies on the association between mortality risk and serum P concentration have been reported. According to a recent study by Kim et al [5], the average serum P concentration of dialysis patients was 5.3 mg/dL. In total, 51% of the patients were maintaining serum P concentration within the KDOQI target range of 3.5–5.5 mg/dL. Furthermore, 40.7% of the patients had their serum P level $>$ 5.5 mg/dL, indicating that serum P concentration is not properly controlled in a substantial number of Korean dialysis patients [5]. Although the supporting evidence is not strong in this country, we recommend that a phosphate binder be administered when serum P concentration is $>$ 5.0 mg/dL.

P removal through dialysis

Although HD has advanced significantly with the development of dialysis membranes and the use of ultrapure dialysate, there are limitations in terms of P removal through dialysis. The kinetics of P differs from those of other low molecular weight substances. Most P exists in the bones or teeth, and only 1% exists in the blood. As a result, the amount of P removed from the body through dialysis is extremely limited.

The amount of P removed by conventional HD (3 times/wk, 4 h/session) is approximately 2.3–2.6 g/wk, and the amount removed by PD (4 times/d, 2-L exchanges) is 2.0–2.2 g per week. If the session length of HD is extended to 5 hours or more, the removal of P increases to 3.0–3.6 g/wk. If nocturnal HD (8 hours/day) is performed, the removal of P can increase to 4.5–4.9 g, which corresponds to twice of that removed by conventional HD [29]. However, the amount of P removed through postdilution hemodiafiltration is 3.0–3.3 g, which is only a small increase compared to conventional HD [16]. Currently, the majority of patients receive conventional dialysis, and only a very small number of patients undergo nocturnal HD or hemodiafiltration in Korea. Thus, if the daily dietary P intake is assumed to be 800 mg, the amount of P removed through weekly conventional dialysis is only half of the dietary intake. Thus, the administration of phosphate binders would be inevitable for controlling the serum P concentration in our dialysis patients.

Use of phosphate binders

The currently available phosphate binders are aluminum-containing phosphate binders, Ca-containing phosphate binders, and non Ca-based phosphate binders. The advantages of aluminum-containing phosphate binders (e.g., aluminum hydroxide) are their excellent phosphate binding capacity and low cost, whereas the drawback is the risk of aluminum accumulation in the body. Due to the risks of aluminum-induced osteomalacia and encephalopathy, the long-term use of aluminum hydroxide is no longer recommended [30].

Ca-containing phosphate binders, either Ca carbonate or Ca acetate, began to be actively used in clinical practice in the 1980s. Although Ca-containing phosphate binders have slightly lower phosphate-binding capacity than aluminum-containing phosphate binders, they are cost-effective and have no risk of aluminum accumulation. However, increased Ca loading and the Ca-P product are linked to hypercalcemia and vascular calcification. In addition, excessive inhibition of iPTH release and development of adynamic bone disease may ensue.

In a recent observational study, the mortality rate was 19% lower in patients using phosphate binders compared to those who did not [31]. However, when the data were adjusted for sex, age, and morbidity, no significant difference in the mortality rate was found between the groups. As such, the relationship between Ca-containing phosphate binders and mortality must be clarified through additional studies.

With respect to non Ca-based phosphate-binders, sevelamer hydrochloride/carbonate and lanthanum carbonate are used in this country. Sevelamer has the advantage of reducing Ca overload, owing to its lack of Ca content as an anion-exchange resin, but has drawbacks of its relatively low phosphate binding capacity and high price. Moreover, sevelamer is known to have additional advantages of decreasing serum cholesterol and uric acid concentration, and it has anti-inflammatory effects. Block et al [32] studied 129 incident HD patients in whom either Ca-containing phosphate binders or sevelamer was administered for 18 months. They found that coronary artery calcification advanced more quickly in patients taking Ca-containing phosphate-binders compared with those receiving sevelamer. Furthermore, when the same patients were monitored through follow-ups for the next 44 months, patients who had been administered sevelamer exhibited a lower mortality rate [33]. By contrast, sevelamer administration did not exhibit a significant difference in mortality compared to Ca-containing phosphate binders in another study involving 2,103 patients [34].

Lanthanum carbonate, a non-Ca-, nonaluminum-containing phosphate binder, is a trivalent metal and is minimally absorbed by gastrointestinal tract. Its phosphate-binding capacity is known to be identical or superior to that of aluminum-containing phosphate binders. However, any potential side effects associated with accumulation within the body are currently unknown.

A previous study, in which lanthanum carbonate and another phosphate binder were randomly assigned to approximately 1,300 HD patients and followed for 2 years, showed that lanthanum had superior medication adherence and efficacy [35]. In PD patients, the serum P level was effectively controlled through high-dosage administration (2,250 mg/day) of lanthanum carbonate [36]. Furthermore, a recent study reported that treatment with lanthanum was independently associated with a significant survival benefit in HD patients with inadequately controlled hyperphosphatemia [37]. Despite

Table 4. Equivalent dosage for dialysis patients switching from calcium acetate to sevelamer or lanthanum

Calcium acetate 667 mg	Sevelamer hydrochloride 400 mg	Sevelamer hydrochloride 800 mg	Lanthanum carbonate 500 mg
1 tablet	2 tablets	1 tablet	0.5 tablets
2 tablets	3 tablets	2 tablets	1 tablet
3 tablets	5 tablets	3 tablets	1.5 tablets

Adapted with permission from: Daugirdas JT, Finn WF, Emmett M, Chertow GM; Frequent Hemodialysis Network Trial Group: The phosphate binder equivalent dose. *Semin Dial* 24: 41–49, 2011.

these encouraging results, however, there have been concerns of potential side effects induced by long-term use of lanthanum. In particular, the development of bone toxicity due to lanthanum accumulation should be closely monitored in patients with long-term lanthanum use. Table 4 shows the equivalent dosage information for cases in which a Ca-containing phosphate binder is switched into a non–Ca-based phosphate binder [38].

Treatment of secondary hyperparathyroidism

We suggest that in CKD stage 5D, serum iPTH levels be maintained within the range of 100–300 pg/mL. To achieve this target range, dialysis patients can be medicated when the iPTH is elevated > 200–300 pg/mL. If the iPTH level is < 150 pg/mL, medications should be reduced. In dialysis patients with an iPTH level < 100 pg/mL, efforts to avoid adynamic bone disease are necessary. Parathyroidectomy is indicated when the iPTH level is persistently > 500 pg/mL, despite appropriate medical treatment.

According to the 2014 Korean NHIS for treating secondary hyperparathyroidism (SHPT), administration of calcitriol is indicated when iPTH is elevated > 200 pg/mL. The KDIGO guidelines recommended that the iPTH level be 2–9 times the normal range (i.e., 130–585 pg/mL, given the upper normal value of 65 pg/mL) [7,11]. By contrast, the target ranges of iPTH are 150–300 and 60–240 pg/mL, according to the KDOQI, and JSDT guidelines, respectively [6,9]. Considering that many Korean HD patients were in the low range of iPTH [5] and that the best survival rate was achieved in Japanese HD patients whose iPTH was approximately 180 pg/mL [28], we believe that the iPTH levels within 100–300 pg/mL would be appropriate in this country. However, the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial failed to demonstrate that effective suppression of iPTH could reduce the risk of death or major cardiovascular events in dialysis patients [39]. Therefore, we currently suggest that the upper allowable limit of iPTH be 500 pg/mL.

The Korean NHIS approves the use of paricalcitol and cinacalcet when iPTH is > 300 pg/mL. However, they ask us to choose calcitriol as the first line drug before prescribing paricalcitol or cinacalcet. We believe that the choice of VDRA should be at the discretion of physicians, and should consider the prior treatment history and current conditions of each patient. The latter include states of serum minerals, bones, and extraskeletal organs. Treatment may be necessary even if the iPTH level does not exceed 300 pg/mL. If the serum Ca exceeds 11 mg/dL, for instance, parathyroid function is partially inhibited and iPTH will not exceed 300 pg/mL. However, hyperparathyroidism treatment is still necessary for the correction of the mineral imbalance. Thus, the current Korean NHIS for restricting treatment should be revised because they serve only to delay surgery and result in cyclic improvements and deteriorations of hyperparathyroidism. By contrast, the ongoing treatment should be reduced if the iPTH level decreases to < 150 pg/mL. A further decrease of iPTH level < 100 pg/mL implies adynamic bone disease and a possibility of extraskeletal calcification, and treatment to suppress iPTH should be stopped. In cases of iPTH > 500 pg/mL, surgical treatment should be considered if appropriate medical treatment is not successful.

Medical treatment

To prevent SHPT, the control of hyperphosphatemia is important using dietary restriction, adequate dialysis, and reasonable phosphate binders. To suppress the excessive parathyroid hormone release, VDRAs (calcitriol, paricalcitol) and/or calcimimetics are useful according to the patient conditions. Surgical treatment should only be indicated for SHPT that cannot be controlled by all efforts with medical treatment.

VDRAs

In predialysis patients, oral calcitriol can be administered if the patient has hypocalcemia or elevated iPTH levels. Intravenous calcitriol (0.5–1.5 μg 1–3 times/wk) can be used for dialysis patients whose iPTH is > 200 pg/mL. Paricalcitol can be administered if iPTH is > 300 pg/mL. When VDRAs are administered, their dosage should be adjusted by measuring serum Ca, P, and iPTH levels every 2–4 weeks.

VDRAs are clinically useful as they act on parathyroid by a feedback mechanism. According to the 2014 Korean NHIS, oral calcitriol is allowed in patients with estimated glomerular filtration rate < 40 mL/min/1.73 m^2. The appropriate weekly dosage is 0.5–1.5 μg. The recommended iPTH levels in the 2003 KDOQI guidelines were < 70 pg/mL in CKD stage 3 and < 110 pg/mL in CKD stage 4 [6]. Furthermore, according to the 2014 Korean NHIS, intravenous calcitriol can be administered if the iPTH level is > 200 pg/mL and the PTH-lowering responses are refractory to oral calcitriol. The typical dosage per dialysis is 0.5–1.5 μg, with the maximum dose being 5 μg. However, because calcitriol increases gastrointestinal absorption of Ca and P and causes increases in the serum Ca and P levels and vascular calcification, more specific drugs targeting the parathyroid gland are under development. Among these new drugs, the third-generation drug paricalcitol is currently used in Korea.

Paricalcitol has the advantage of inducing less hypercalcemia in patients with SHPT, and has been shown to decrease the cardiovascular morbidity and mortality in an observational study [40]. In patients with iPTH levels > 300 pg/mL, a smaller initial dose of paricalcitol is chosen between iPTH/120 and 0.04–0.1 μg/kg. The dose may be adjusted at 2–4 week intervals, based on relationship between subsequent iPTH levels and baseline iPTH level, up to 0.24 μg/kg per dialysis. When the dosage is increased until an initial response is observed, it is recommended that the levels of Ca and P be measured at least once every 2 weeks (up to twice a week). When the iPTH levels reach the target range, the dose of paricalcitol can gradually be reduced. The initial dose of

paricalcitol is usually 2–5 μg per dialysis, and the dosage during maintenance can gradually be decreased by 1–2 μg per dialysis (1/3 or 1/4 of dosage), while the iPTH and mineral levels are monitored [6]. If the iPTH level is < 150 μg/mL, the administration should be reduced or halted. If the iPTH level is < 100 pg/mL, discontinuation of VDRAs should be considered. After halting the treatment, if iPTH increases to > 100 pg/mL, the drug can be re-administered with a half of dosage used before the treatment was halted. If the drug was already administered at a minimum dosage prior to halting the treatment, the intervals of drug administration can be adjusted to once every two administrations [6]. If the drug administration is halted at iPTH < 300 pg/mL according to the 2014 Korean NHIS, the iPTH level will rebound, necessitating a higher dosage during re-administration. The resultant fluctuations of iPTH may lead to progressive hyperparathyroidism, and we believe the drug maintenance guidelines by the Korean NHIS should be revised.

Cinacalcet

Cinacalcet can be administered if the iPTH level is > 300 pg/mL. The initial dosage is 25 mg and should be administered during dinner. When cinacalcet is administered or its dosage is changed, serum Ca measurement should be considered at the next dialysis session. In addition, P and iPTH should be measured every 3 or 4 weeks to adjust the dosage.

Calcimimetics decrease PTH by transmitting signals into the cells from parathyroid Ca sensing receptors. As Ca sensing receptors exist not only in the parathyroid, but also in the vessels and other organs, calcimimetics are predicted to play a protective role in the cardiovascular system. Calcimimetics are particularly useful in patients with SHPT with increased Ca and P levels. The bioavailability of cinacalcet is low (20–25%), and the first-pass effect of cinacalcet in the liver is large. Thus, it is recommended to be taken with food, as this increases its bioavailability by 1.5–1.8 times [41]. As the peak blood concentration is reached 2–6 hours after drug administration, its effect can be properly evaluated by the blood test conducted in the following morning if the drug is taken during dinner [41]. The recommended drug dosage is from 25 mg and can be increased by 25 mg every 3 or 4 weeks, up to 100 mg. Typical adverse events include hypocalcemia and gastrointestinal symptoms (nausea, vomiting, diarrhea, etc.). Thus, monitoring of hypocalcemia is necessary while cinacalcet is administered. The monitoring intervals are determined based on the serum Ca level of the patients. The Ca level should be measured immediately before the next dialysis session. According to the 2014 Korean NHIS, cinacalcet is initially indicated when iPTH is > 300 pg/mL and serum Ca is > 9.0 mg/dL. The dosage can be increased if Ca is > 8.4 mg/dL. It can be maintained without being increased when the Ca level is > 7.5 mg/dL, but it should not be administered when the Ca level is < 7.5 mg/dL.

Calcimimetics can be used alone or administered combined with VDRAs, including calcitriol, when necessary. Similar to paricalcitol, the administration of calcimimetics is recommended to be stopped if iPTH is < 300 pg/mL according to the 2014 Korean NHIS. This strategy will lead to the iPTH rebound, consequently requiring a greater dosage of calcimimetics. Thus, the Korean NHIS regarding drug maintenance should be revised to decrease the risks of parathyroidectomy, cardiovascular complications, and bone disorders due to SHPT.

Selection of VDRAs and/or cinacalcet, based on the serum Ca levels

Calcitriol should be considered first if the serum Ca is < 8.4 mg/dL. If the serum Ca is 8.4–9.0 mg/dL, calcitriol or paricalcitol can be administered depending on the serum P level. If the serum Ca is 9.0–10.2 mg/dL, paricalcitol and cinacalcet are preferred. Depending on the serum Ca and P levels, the drugs should be taken alone or as combination therapy. If the serum Ca is > 10.2 mg/dL, cinacalcet should be primarily considered. Paricalcitol may also be considered as a part of combination therapy depending on the serum Ca and P levels.

Serum Ca < 8.4 mg/dL

In this situation, correcting hypocalcemia should be a priority because the increase in PTH is a physiological compensatory phenomenon. Calcitriol is the primary treatment option at daily doses of 0.25-0.5 μg depending on the serum Ca concentration. For treatment of hypocalcemia, daily oral administration is better than pulse intermittent therapy. After the serum Ca level is normalized, the iPTH level should be followed for re-evaluation. If the serum P is > 5.0 mg/dL, a phosphate binder should be combined.

Serum Ca 8.4–9.0 mg/dL

Either calcitriol or paricalcitol can be used. We suggest calcitriol and paricalcitol in patients with serum P < 5.0 and ≥ 5.0 mg/dL, respectively. In both cases, appropriate phosphate binders may be added. The Korean NHIS demands that oral calcitriol should be the first choice of hyperparathyroidism treatment in the patients with iPTH > 200 pg/mL, and that intravenous calcitriol can be administered when the oral administration is ineffective because of the cost difference. Although the efficacy is not affected by the route of administration, the drug compliance may be enhanced by intravenous use. However, the intermittent pulse dosage, for instance, three times a week, is more advantageous than the daily administration of calcitriol because of less hypercalcemia and hyperphosphatemia. Although a dosage of up to 5 μg is possible during dialysis, the practical oral and intravenous doses of calcitriol are 0.25–0.75 μg and 0.5–1.0 μg, respectively, due to the risk of hypercalcemia and hyperphosphatemia [6]. If the iPTH level is persistently > 300 pg/mL despite the use of calcitriol, paricalcitol would be the alternative. Paricalcitol may also be superior to calcitriol in patients with overt hyperphosphatemia.

Serum Ca 9.0–10.2 mg/dL

Paricalcitol and cinacalcet are preferred to calcitriol because of the risk of hypercalcemia and vascular calcification. When the serum P level is < 2.4 mg/dL, paricalcitol is the best option because cinacalcet may further reduce the serum P. Depending on the serum Ca and P levels, paricalcitol and cinacalcet can be administered alone or as combination therapy.

Serum Ca > 10.2 mg/dL

Cinacalcet is preferred to pericalcitol. In patients with the serum P < 2.4 mg/dL, however, cinacalcet may not be useful because it can further reduce the serum P level. Depending on the serum Ca and P levels, paricalcitol and cinacalcet can be administered alone or as combination therapy.

Surgical treatment

Parathyroidectomy should be considered if the following three findings persist despite appropriate medical treatments: (1) iPTH > 500 pg/mL; (2) parathyroid > 500 mm^3 in size upon ultrasonography; and (3) uncontrollable hypercalcemia and hyperphosphatemia, X-ray findings of a bone disorder, severe bone and muscle pain, calciphylaxis, or soft tissue calcification. Preoperative parathyroid imaging to localize the lesion is necessary. The surgical method should be determined based on the overall status of the patient, the future plan of kidney transplantation, and the presence of thyroid pathology.

SHPT that cannot be managed by medical treatment requires surgical treatment. Although ethanol or calcitriol can be injected into the parathyroid gland for ablation, the high risk of recurrence and a possibility of adhesion are anticipated. Hence, surgery is preferred as long as an experienced surgeon is available. Future plans of kidney transplantation and cardiovascular status of the patient will determine the methods of surgery and anesthesia. Although subtotal parathyroidectomy and total parathyroidectomy with autotransplantation are the representative surgical methods, limited parathyroidectomy, single parathyroidectomy, or total parathyroidectomy without autotransplantation can also be performed, depending on the situations [42]. In exceptional cases, parathyroidectomy may be performed through local anesthesia if the patient is at a high risk for general anesthesia-related complications. The localization of parathyroid glands is important in preoperative evaluation. Parathyroid imaging methods include sestamibi parathyroid scans, neck ultrasound, and neck computed tomography scans.

The specific findings of medical treatment failure, indicative of parathyroidectomy, include the following: (1) iPTH > 500 pg/mL; (2) parathyroid > 500 mm^3 in size, as determined by ultrasonography; and (3) unmanageable hypercalcemia and hyperphosphatemia, X-ray findings of a bone disorder, severe bone and muscle pain, calciphylaxis, or soft tissue calcification. If all these three findings are present after all avenues of medical treatment, surgical treatment should be applied [43].

Because the major postoperative complication is hypocalcemia, serum Ca levels should be monitored every 4–6 hours for 48–72 hours after surgery. Subsequently, the serum Ca level should be measured twice daily. If the ionized Ca is < 3.6 mg/dL and the corrected total Ca is < 7.2 mg/dL, 10 mL of 10% Ca gluconate containing 90 mg of Ca should be administered at a rate of 1–2 mg/kg/h. Eventually, the ionized Ca should be maintained within a range of 4.6–5.4 mg/dL [6]. Phosphate binders, if used, should be replaced by calcium carbonate 1–2 g three times (between meals) a day for the purpose of Ca supplementation. Calcitriol should be administered in addition to intravenous Ca until the serum Ca reaches the target range. When oral administration of Ca is possible, the patient can be treated as an outpatient. Recurrence is possible if kidney transplantation is not undertaken, and close monitoring is recommended.

Conclusion

Abnormal Ca and P metabolism leading to the development of SHPT and cardiovascular calcification can be complicated during the early course of CKD, when glomerular filtration rate falls < 60 mL/min/1.73 m^2. Thus, early interventions to correct abnormal Ca and P metabolism are important to reduce cardiovascular morbidity and mortality. However, many dialysis patients in Korea were reported to have out-of-range levels for serum Ca, P, and iPTH. Because we do not have our own practice guidelines for the management of CKD-MBD, we may need to adapt the major international guidelines and update the evidence-based medicine in this practice area.

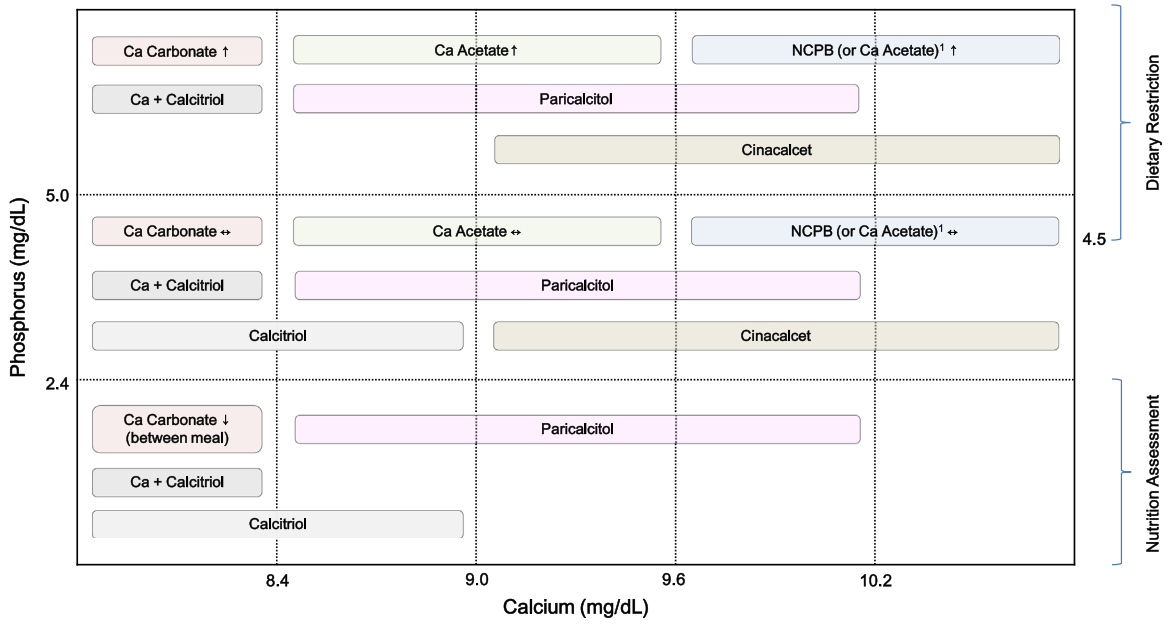

Figure 1. Summary of the treatment strategy for control of secondary hyperparathyroidism according to the level of serum calcium and phosphorus.
[1]NCPB, non–calcium-based phosphate binder, is reimbursed for P ≥ 5.5 mg/dL, and Ca-P ≥ 55 mg^2/dL^2 (according to the Korean National Health Insurance Standards, as of July 2014).

Additionally, we should follow the guidance of the Korean NHIS. Considering these current situations, Fig. 1 summarizes our recommendation for the optimal treatment of abnormal serum Ca and P and SHPT. Large-scale, well-designed clinical studies are required to support our strategies to control CKD-MBD in Korea. Based on such data, our practice guidelines could be developed and better long-term outcomes should be anticipated in our dialysis patients.

Conflict of interest

The authors have served on an advisory panel for AbbVie Korea.

References

[1] Block GA, Hulbert-Shearon TE, Levin NW, Port FK: Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis* 31:607–617, 1998

[2] Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK: Association of elevated serum PO_4, Ca $\times$ PO_4 product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol* 12:2131–2138, 2001

[3] Kestenbaum B, Sampson FN, Rudser KD, Patterson DJ, Seliger SL, Young B, Sherrard DJ, Andress DL: Serum phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol* 16:520–528, 2005

[4] Jin DC, Ha IS, Kim NH, Lee SW, Lee JS, Yoon SR, Kim BS: Brief Report: Renal replacement therapy in Korea, 2010. *Kidney Res Clin Pract* 31:62–71, 2012

[5] Kim GH, Choi BS, Cha DR, Chee DH, Hwang E, Kim HW, Chang JH, Kim JK, Noh JW, Joo KW, Lee SC, Han SW, Kim S, Kim SW, Shin SK, Park W, Kim W, Huh W, Kwon YJ, Kang YS: Serum calcium and phosphorus levels in patients undergoing maintenance hemodialysis: A multicentre study in Korea. *Kidney Res Clin Pract* 33:52–57, 2014

[6] National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*;42(4 Suppl 3):S1–S201, 2003

[7] Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl* 113:S1–S130, 2009

[8] Elder G, Faull R, Branley P, Hawley C, Caring for Australasians with Renal Impairment (CARI). The CARI guidelines. Management of bone disease, calcium, phosphate and parathyroid hormone. *Nephrology (Carlton)* 11:S230–S261, 2006

[9] Fukagawa M, Yokoyama K, Koiwa F, Taniguchi M, Shoji T, Kazama JJ, Komaba H, Ando R, Kakuta T, Fujii H, Nakayama M, Shibagaki Y, Fukumoto S, Fujii N, Hattori M, Ashida A, Iseki K, Shigematus T, Tsukamoto Y, Tsubakihara Y, Tomo T, Hirakata H, Akizawa T, CKD-MBD Guideline Working Group; Japanese Society for Dialysis Therapy. Clinical practice guideline for the management of chronic kidney disease-mineral and bone disorder. *Ther Apher Dial* 17:247–288, 2013

[10] Steddon S, Sharples E: Renal Association Clinical Practice Guideline in mineral and bone disorders in CKD. *Nephron Clin Pract* 118: c145–c152, 2011

[11] Goldsmith DJ, Covic A, Fouque D, Locatelli F, Olgaard K, Rodriguez M, Spaovski G, Urena P, Zoccali C, London GM, Vanholder R: Endorsement of the Kidney Disease Improving Global Outcomes (KDIGO) Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guidelines: a European Renal Best Practice (ERBP) commentary statement. *Nephrol Dial Transplant* 25:3823–3831, 2010

[12] Toussaint N, Cooney P, Kerr PG: Review of dialysate calcium concentration in hemodialysis. *Hemodial Int* 10:326–337, 2006

[13] Maynard JC, Cruz C, Kleerekoper M, Levin NW: Blood pressure response to changes in serum ionized calcium during hemodialysis. *Ann Intern Med* 104:358–361, 1986

[14] van der Sande FM, Cheriex EC, van Kuijk WH, Leunissen KM: Effect of dialysate calcium concentrations on intradialytic blood pressure course in cardiac-compromised patients. *Am J Kidney Dis* 32:125–131, 1998

[15] Kopple JD, Coburn JW: Metabolic studies of low protein diets in uremia. II. Calcium, phosphorus and magnesium. *Medicine (Baltimore)* 52:597–607, 1973

[16] Cupisti A, Kalantar-Zadeh K: Management of natural and added dietary phosphorus burden in kidney disease. *Semin Nephrol* 33:180–190, 2013

[17] Noori N, Kalantar-Zadeh K, Kovesdy CP, Bross R, Benner D, Kopple JD: Association of dietary phosphorus intake and phosphorus to protein ratio with mortality in hemodialysis patients. *Clin J Am Soc Nephrol* 5:683–692, 2010

[18] Kalantar-Zadeh K, Gutekunst L, Mehrotra R, Kovesdy CP, Bross R, Shinaberger CS, Noori N, Hirschberg R, Benner D, Nissenson AR, Kopple JD: Understanding sources of dietary phosphorus in the treatment of patients with chronic kidney disease. *Clin J Am Soc Nephrol* 5:519–530, 2010

[19] Fouque D, Vennegoor M, Ter Wee P, Wanner C, Basci A, Canaud B, Haage P, Konner K, Kooman J, Martin-Malo A, Pedrini L, Pizzarelli F, Tattersall J, Ordoir J, Vanholder R: EBPG guideline on nutrition. *Nephrol Dial Transplant*(22 Suppl 2):ii45–ii87, 2007

[20] Kalantar-Zadeh K: Patient education for phosphorus management in chronic kidney disease. *Patient Prefer Adherence* 7:379–390, 2013

[21] Shinaberger CS, Greenland S, Kopple JD, Van Wyck D, Mehrotra R, Kovesdy CP, Kalantar-Zadeh K: Is controlling phosphorus by decreasing dietary protein intake beneficial or harmful in persons with chronic kidney disease? *Am J Clin Nutr* 88:1511–1518, 2008

[22] Lynch KE, Lynch R, Curhan GC, Brunelli SM: Prescribed dietary phosphate restriction and survival among hemodialysis patients. *Clin J Am Soc Nephrol* 6:620–629, 2011

[23] Martin KJ, Gonzalez EA: Prevention and control of phosphate retention/hyperphosphatemia in CKD-MBD: what is normal, when to start, and how to treat? *Clin J Am Soc Nephrol* 6:440–446, 2011

[24] Jono S, McKee MD, Murry CE, Shioi A, Nishizawa Y, Mori K, Morii H, Ciachelli CM: Phosphate regulation of vascular smooth muscle cell calcification. *Circ Res* 87:E10–E17, 2000

[25] Ciceri P, Volpi E, Brenna I, Arnaboldi L, Neri L, Brancaccio D, Cozzolino M: Combined effects of ascorbic acid and phosphate on rat VSMC osteoblastic differentiation. *Nephrol Dial Transplant* 27:122–127, 2012

[26] Koleganova N, Piecha G, Ritz E, Schirmacher P, Müller A, Meyer HP, Gross ML: Arterial calcification in patients with chronic kidney disease. *Nephrol Dial Transplant* 24:2488–2496, 2009

[27] Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM: Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol* 15:2208–2218, 2004

[28] Taniguchi M, Fukagawa M, Fujii N, Hamano T, Shoji T, Yokoyama K, Nakai S, Shigematsu T, Iseki K, Tsubakihara Y, Committee of Renal Data Registry of the Japanese Society for Dialysis Therapy. Serum phosphate and calcium should be primarily and consistently controlled in prevalent hemodialysis patients. *Ther Apher Dial* 17:221–228, 2013

[29] Cupisti A, Gallieni M, Rizzo MA, Caria S, Meola M, Bolasco P: Phosphate control in dialysis. *Int J Nephrol Renovasc Dis* 6:193–205, 2013

[30] Alfrey AC: Aluminum toxicity in patients with chronic renal failure. *Ther Drug Monit* 15:593–597, 1993

[31] Winkelmayer WC, Liu J, Kestenbaum B: Comparative effectiveness of calcium-containing phosphate binders in incident U.S. dialysis patients. *Clin J Am Soc Nephrol* 6:175–183, 2011
[32] Block GA, Spiegel DM, Ehrlich J, Mehta R, Lindbergh J: hemodialysis. *Kidney Int* 68:1815–1824, 2005
[33] Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM: Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. *Kidney Int* 71:438–441, 2007
[34] Suki WN: Effects of sevelamer and calcium based phosphate binders on mortality in hemodialysis patients: results of a randomized clinical trial. *J Ren Nutr* 18:91–98, 2008
[35] Finn WF, SPD 450-307 Lanthanum Study Group. Lanthanum carbonate versus standard therapy for the treatment of hyperphosphatemia: safety and efficacy in chronic maintenance hemodialysis patients. *Clin Nephrol* 65:191–202, 2006
[36] Hutchison AJ, Gill M, Copley JB, Poole L, Wilson RJ: Lanthanum carbonate versus placebo for management of hyperphosphatemia in patients undergoing peritoneal dialysis: a subgroup analysis of a phase 2 randomized controlled study of dialysis patients. *BMC Nephrol* 14:40, 2013
[37] Komaba H, Kakuta T, Suzuki H, Hida M, Suga T, Fukagawa M: Survival advantage of lanthanum carbonate for hemodialysis patients with uncontrolled hyperphosphatemia. 10.1093/ndt/gfu335. Epub 2014 Nov 23. *Nephrol Dial Transplant* 30:107–114, 2015
[38] Daugirdas JT, Finn WF, Emmett M, Chertow GM, Frequent Hemodialysis Network Trial Group. The phosphate binder equivalent dose. *Semin Dial* 24:41–49, 2011
[39] Chertow GM, Block GA, Correa-Rotter R, Drüeke TB, Floege J, Goodman WG, Herzog CA, Kubo Y, London GM, Mahaffey KW, Mix TC, Moe SM, Trotman ML, Wheeler DC, Parfrey PS, EVOLVE Trial Investigators. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med* 367:2482–2494, 2012
[40] Teng M, Wolf M, Lowrie E, Ofsthun N, Lazarus JM, Thadhani R: Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. *N Engl J Med* 349:446–456, 2003
[41] Verheyen N, Pilz S, Eller K, Kienreich K, Fahrleitner-Pammer A, Pieske B, Ritz E, Tomaschitz A: Cinacalcet hydrochloride for the treatment of hyperparathyroidism. *Expert Opin Pharmacother* 14:793–806, 2013
[42] Dumasius V, Angelos P: Parathyroid surgery in renal failure patients. x–xi. *Otolaryngol Clin North Am* 43:433–440, 2010
[43] Tominaga Y, Matsuoka S, Uno N: Surgical and medical treatment of secondary hyperparathyroidism in patients on continuous dialysis. *World J Surg* 33:2335–2342, 2009