

A Japanese approach for CKD-MBD

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Disturbances in mineral and bone metabolism have a critical role in the pathogenesis of cardiovascular complications in patients with chronic kidney disease (CKD). The term 'renal osteodystrophy' has recently been replaced by 'CKD-mineral and bone disorder (CKD-MBD)', which includes abnormalities in bone and mineral metabolism and vascular calcification. The Japanese Society for Dialysis Therapy clinical practice guideline for the management of secondary hyperparathyroidism in chronic dialysis patients was originally published in Japanese in 2006, then in English in 2008. During the past 5 years, this first guideline has contributed to a considerably better understanding and control of secondary hyperparathyroidism in CKD patients by physicians, other medical professionals, and the patients themselves. However, since its publication several new therapeutic modalities have become available for Japanese dialysis patients, which added more evidence to this area. Thus, we revised the guideline to include several new policies, and the new guideline was published in Japanese in 2012. This article contains the new guideline text, and clinical significance of CKD-MBD in Japan.

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Abnormalities of mineral and bone metabolism in patients with chronic kidney disease (CKD) have traditionally been assessed and managed in terms of renal osteodystrophy. However, it has been demonstrated that abnormal mineral and bone metabolism in CKD not only leads to bone lesions but may also influence vital prognosis by causing ectopic calcification throughout the body, including the blood vessels over the long term. Consequently, it has been proposed that the conventional term renal osteodystrophy should be used for bone lesions only, and a new concept of CKD-related mineral and bone disorder (MBD) has been introduced.¹ This paradigm shift of the disease concept has resulted from research on evidence-based medicine mainly performed since 1990 and the publication of guidelines based on such research. Evidence-based medicine studies have used survival as the main outcome measure in a large number of cases,^{2–12} and it has become evident that the CKD-related MBD is deeply involved in the prognosis of dialysis patients.

The dialysis population in Japan has reached 300,000 in 2013 (according to the Japanese Society for Dialysis Therapy (JSDT) registry data; <http://docs.jsdt.or.jp/overview/index.html>). The proportions of aged dialysis patients and those with long dialysis vintage are steadily increasing, which makes management of vascular calcification and parathyroid function increasingly more important. In Japan, the prevalence of hypoalbuminemia in dialysis patients is high, and in these patients blood total calcium concentration is relatively lower with respect to ionized calcium concentration than in dialysis patients with normal serum albumin levels. As ionized calcium, not total calcium concentration, is a marker of bioactivity, adjustment by serum albumin is necessary. With regard to the timing of blood sampling for patients who have a typical dialysis prescription of three times a week, pre-dialysis serum phosphorus and calcium levels are higher at the beginning of the week than at mid-week and end-week dialysis sessions, due to the longer time interval between sessions over the week-end. By convention, in Japan blood sampling is done 3 days after the preceding dialysis session (i.e., on Monday or Tuesday). This means that serum phosphorus levels, in particular, are significantly higher than when measured before a mid-week session.¹³ The JSDT clinical practice guideline for the management of secondary hyperparathyroidism in chronic dialysis patients was originally published in

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Japanese in 2006, then in English in 2008.¹⁴ This guideline emphasizes on improving patient survival, and it was one of the first guidelines in this therapeutic field, preceding the Kidney Disease: Improving Global Outcomes (KDIGO) guideline.¹⁵ The CKD-MBD guidelines are highly specific in that they have established target levels for three parameters, namely serum phosphorus, calcium, and parathyroid hormone (PTH). Accounting for their interactions, it is necessary to set an order of priority for the clinical management, starting with serum phosphorus, then serum calcium, and finally serum PTH, as stated in the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines, which are one of the first guidelines in CKD-MBD.¹⁶ However, the treatment algorithm proposed by the K/DOQI guidelines is too complicated. For example, they suggest that serum phosphorus and PTH levels be re-assessed after measurement of the calcium-phosphorus product (CaxP). Because CaxP product and serum phosphorus are strongly correlated, adequate control of serum phosphorus and calcium should result in a suitable level of CaxP product. Therefore, in order to keep our treatment algorithm simple, we did not adopt a target range for CaxP product in the Japanese guideline, but instead, focused more on phosphorus and calcium levels.¹⁷ Achieving calcium and phosphorus levels within the target range will, in turn, lead to a suitable level of CaxP product.¹⁸ The Japanese guideline uses a treatment algorithm based on optimal control of serum phosphorus and calcium levels (Figure 1). This allows relatively wide target ranges for phosphorus and calcium and provides more flexibility than narrow target ranges, which will reduce the possibility to control PTH. Guideline target ranges for serum P, Ca, and PTH levels are based on survival data of Japanese dialysis patients. In addition, considering that Japanese dialysis patients tend to have a longer dialysis vintage than their American and European counterparts, we propose that parathyroid control be done at an early stage of CKD in this patient population.

After its initial release, the first guideline has contributed to considerably improved understanding and better control of secondary hyperparathyroidism in CKD patients by physicians, other medical professionals, and by the patients themselves.¹⁹ Thus, we have added new areas of discussion on CKD-MBD, which were not covered in the first guideline.²⁰ These include vascular calcification, amyloid bone disease, peritoneal dialysis, pediatric CKD, pre-dialysis CKD, and kidney transplantation. For this purpose, we collaborated with specialists from relevant societies, especially the Japanese Society of Nephrology.

Nevertheless, in this revised guideline the basic policy of the previous version has been retained. Thus routine blood biochemistry examinations are done regularly in dialysis practice, whereas specific examinations are only performed in accordance with specific situations. We recommend that both patient evaluation and therapeutic plans be based on trends of biochemistry results, as shown by repeat measurements, and not on a single laboratory test result.

CONTROL OF SERUM PHOSPHORUS AND CALCIUM

The target range for serum phosphorus was set at 3.5–6.0 mg/dl in the new Japanese guideline. A number of reports have been published concerning the validation of target ranges for serum phosphorus and calcium concentrations. These studies, mainly from the Western world, have largely used mortality as a primary end point.^{2–12} However, in the 2012 JSDT guideline, we have defined target serum phosphorus/calcium ranges according to the results of an analysis of data from the JSDT patient registry, where patients were treated in accordance with the previous JSDT guideline.^{17,21} Following the first release of the guideline in 2006 and increased awareness about CKD-MBD in Japan, new drugs such as cinacalcet hydrochloride and lanthanum carbonate have been available in clinical practice. Accordingly, data from 128,125 dialysis patients, who were monitored from the end of 2006 to the end of 2009, were analyzed. In addition to analytic model used for the previous baseline model (B) (with a 3-year life expectancy), time-dependent (TD) and time averaged (TA) models were used to set target levels for serum phosphorus/calcium and PTH, using mortality as an end point.

Accordingly, we have set the target range for serum phosphorus in dialysis patients at 3.5–6.0 mg/dl. In the KDOQI guidelines, the range was set at 3.5–5.5 mg/dl while the more recent KDIGO guideline on CKD-MBD of 2009¹⁵ recommended that the serum phosphorus level should be lowered towards normal if higher than the reference level. We derived the target level by stratifying serum phosphorus levels in our data set, and this analysis produced a J-shaped curve, in that mortality was found to be increased with both hyperphosphatemia and hypophosphatemia. When $P < 0.01$ was used to indicate statistical significance, the recommended target range was 3.6–5.0 mg/dl for model B, 4.1–6.0 mg/dl for model TD, and 4.1–5.5 mg/dl for model TA. When a hazard ratio (HR) of > 1.2 was considered statistically significant, the recommended range was 3.1–6.0 mg/dl for model B, 3.6–6.5 mg/dl for model TD, and 4.1–6.0 mg/dl for model TA. Model TD characteristically reflects a relatively short-term prognosis, whereas model TA reflects a relatively long-term prognosis. Regardless of the differences between these models, the results were generally similar. Therefore, we continue to recommend a serum phosphorus target range between 3.5 and 6.0 mg/dl, in accordance with our previous guidelines.¹⁶

We recommend that the target range for serum calcium be between 8.4 and 10.0 mg/dl. The KDOQI guidelines state that serum calcium levels be 8.4–9.5 mg/dl, while KDIGO recommends a target within the normal range. Serum calcium levels were validated in the same way as phosphorus levels. When the significance level was set at $P < 0.01$, the recommended range was determined to be ≤ 9.0 mg/dl for model B, ≤ 9.0 mg/dl for model TD, and 8.6–9.5 mg/dl for model TA. When a HR of > 1.2 was considered statistically significant, the recommended range was ≤ 10.0 mg/dl for model B, ≤ 9.0 mg/dl for model TD, and 8.1–10.0 mg/dl for model TA. Unlike with serum phosphorus concentrations, the risk of mortality increased in a linear pattern for both

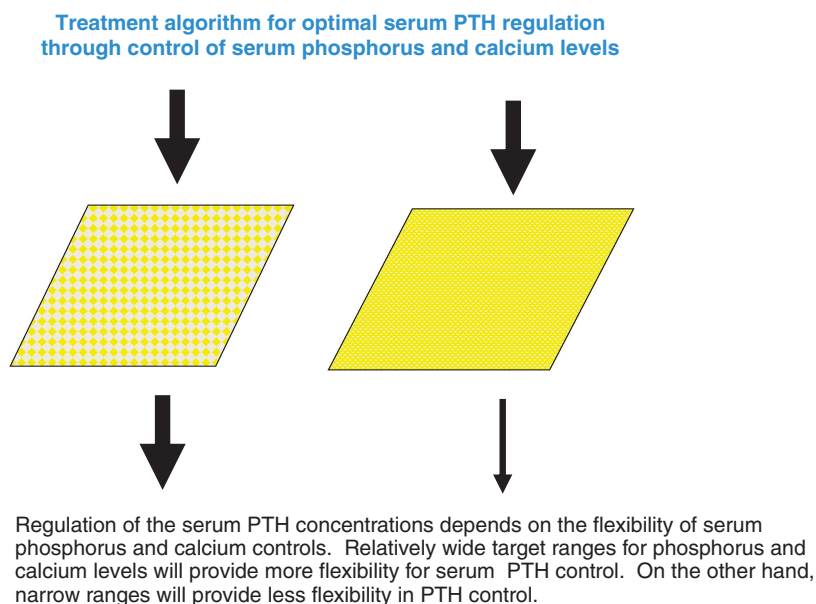


Figure 1 | Treatment algorithm for optimal serum parathyroid hormone (PTH) regulation through control of serum phosphorus and calcium levels. The Japanese guideline uses a treatment algorithm for the serum PTH regulation based on control of serum phosphorus and calcium levels. If target P and Ca ranges are achieved, then start controlling serum PTH. Wider target ranges for serum Pi and Ca provide more flexibility, while narrower target ranges make the treatment of high PTH levels more difficult.

models B and TD. There is still scope for discussion concerning the elimination of the lower limit, and based on the J-shaped curve from modeled TA results and the reference level for healthy people, we consider that 8.4–10.0 mg/dl should be used as the target level, in accordance with previous guidelines. Nevertheless, this statistical validation using data from the JSDT patient database indicates that serum calcium concentrations in patients on dialysis should be maintained at the lowest possible level.^{20–22}

From the previous guidelines, a nine-section chart has been adopted as the treatment tool for keeping serum levels of serum phosphorus and calcium at optimal levels. In each of the nine categories, methods for adjusting the dose of pharmacological medications to keep serum phosphorus and corrected calcium levels within the target range are provided. To validate the recommendations published in our previous guideline, we used the same JSDT patient registry data set to project the 3-year prognosis for patients in each of the nine categories. In addition, target concentrations for serum calcium and phosphorus from the previous guideline were used in the revised version. The results showed that the risk of mortality decreased in the group with normal serum calcium/phosphorus levels and in the group with normal serum phosphorus plus low calcium levels. These findings indicate that the prognosis improves when both serum phosphorus and calcium are kept within the target range. When we examined the relationship between the frequency of attaining target serum phosphorus/calcium levels and prognosis from 2006 to the end of 2008, we found that the more frequently the target level was attained the lower was the mortality risk. This suggests that constant maintenance of serum phosphorus/calcium levels within the target ranges leads to improvement

in life expectancy. Based on these findings, we recommend prompt treatment change when the serum phosphorus or corrected calcium levels are constantly high.^{20,22}

Figure 2 shows treatment/control methods for each part of the nine-section chart. The general objective is that when serum phosphorus levels are high we suggest that a sufficient dialysis dose be ensured and that patients are instructed to reduce their dietary phosphorus intake. Also, it is important to assess the nutritional state, including the amount of food eaten, when serum phosphorus levels are low. Once these precautions are taken, we suggest that pharmacological therapy should be started to control the mineral parameters in the following order of priority: serum phosphorus, calcium, and PTH. In cases with high serum phosphorus levels, the start/increase of a phosphorus binder should be considered, and treatment with active vitamin D sterols should be reduced/suspended depending upon each patient's condition. When a phosphate binder is prescribed, patient compliance must be confirmed. Furthermore, it is important to bear in mind that certain drugs are more effective when taken at specific times. For instance, sevelamer hydrochloride should be taken before a meal, and CaCO_3 and lanthanum carbonate should be taken immediately after a meal. As the efficacy of CaCO_3 is influenced by gastric pH, co-administration of a gastric secretion inhibitor may weaken the drug's efficacy.²³ Lanthanum carbonate, a chewable tablet, should always be chewed, and if an elderly person cannot chew the tablet, it should be crushed and administered orally. If the serum phosphorus level is low, reduction/suspension of phosphorus binder should be considered, and starting/increasing active vitamin D could be considered in some cases.

A user friendly example of how to treat hypercalcemia and hyperphosphatemia by adjusting relevant medications

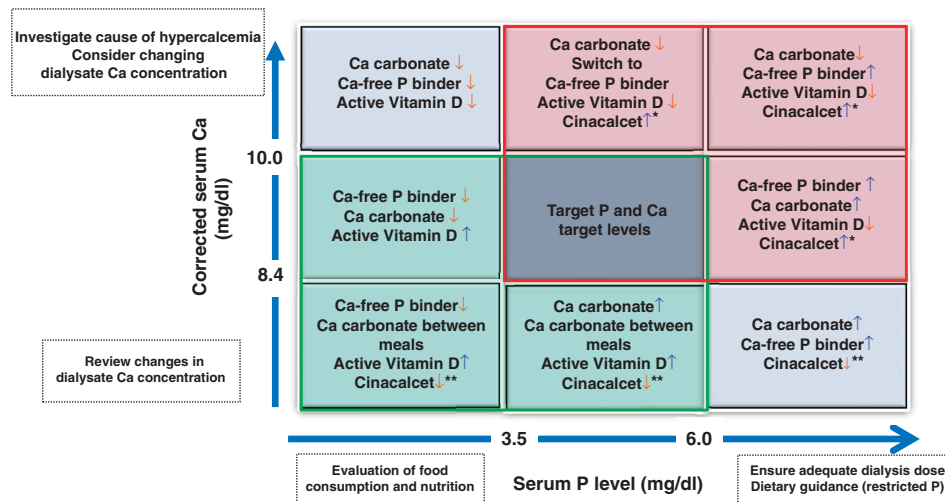


Figure 2 | A user-friendly example of how to treat hypercalcemia and hyperphosphatemia by adjusting relevant medications modified with permission, see ref. 20. To achieve the strike zone here, we should modify therapeutic modalities depending upon each zone. Nine tentative clinical scenarios (1–9) are shown, which indicate how serum phosphorus and corrected serum calcium levels can be used to guide the selection of different therapeutic modalities. When PTH is high and P or Ca is normal to high (area around red line), administration of cinacalct should be considered, and administration of active vitamin D derivative should be contemplated when P or Ca is normal to low high (area around green line). ↑ = start or increase of treatment and ↓ = reduction or suspension of treatment where serum PTH is high* and low**. Ca, serum calcium; CaCO₃, precipitated calcium carbonate; Cinacalct, cinacalct hydrochloride; NCPB, non-calcium-containing phosphorus binder (calcium-free phosphorus binder); P, serum phosphorus.

When serum calcium is high, dose reduction/discontinuation of active vitamin D sterols and/or CaCO₃ should be considered. When a concurrently high measured PTH level is observed, starting cinacalct hydrochloride treatment or increasing the dose is recommended. If hypercalcemia persists, the reason for the lack of improvement should be sought, and a change in dialysate calcium concentration should be considered. When the serum calcium level is low, starting treatment with/increasing the dose of active vitamin D derivatives and/or CaCO₃ should be contemplated, and if cinacalct hydrochloride is being administered, the dose may need to be reduced/discontinued. Administration of CaCO₃ between meals is also effective, because it increases the serum calcium level. The addition of cinacalct hydrochloride to this nine-section chart is a change from the previous guideline. Although cinacalct hydrochloride is mainly used to suppress PTH, it is included in the cases in which the PTH level is high (or low), because cinacalct hydrochloride simultaneously lowers serum phosphorus/calcium levels,^{24,25} and PTH control and serum phosphorus/calcium control are closely linked. In other words, administering cinacalct hydrochloride as a method to control the serum calcium or phosphorus level is advisable for patients with high serum PTH levels. Nevertheless, several precautions need to be taken. First, when cinacalct hydrochloride is going to be administered, it is reasonable to maintain the corrected serum calcium at levels 9.0 mg/dl in order to avoid excessive hypocalcemia. Moreover, any assessment should take into account that

serum PTH is lowest 4–8 h after cinacalct administration and the calcium level is lowest after 8–12 h^{26,27} (Table 1).

ASSESSMENT AND MANAGEMENT OF PARATHYROID FUNCTION

In this new Japanese guideline, intact PTH (iPTH) target level was set at 60–240 pg/ml. Parathyroid function generally increases along with the decline in kidney function. Although the normal range of iPTH is 10–65 mg/ml with the chemiluminescence enzyme immunoassay method, the levels in patients with CKD stage 5 generally exceed it.²⁸ However, as the end-organ action of PTH is reduced in CKD, a PTH level within the normal range would actually reflect the presence of a hypoparathyroid state.²⁹ The previous JSDT guideline set the recommended range of iPTH between 60 and 180 pg/ml, in order to drive parathyroid function towards a more suppressed state. Our re-analysis revealed that PTH levels slightly higher than those previously thought to be optimal should be recommended, as supported by several clinical studies.^{11,12,30} Based on these findings, we recommend that the upper limit of the target range should be raised above that of the previous guideline. The KDIGO guideline set the target range for parathyroid function in dialysis patients to circulating PTH levels between two and nine times greater than the upper limit of the normal reference range in the general population.¹⁴ However, as all clinical studies mentioned above only analyzed a relatively short-term survival, it is uncertain whether guidelines based on these results would be beneficial in terms of long-term

Table 1 | Characteristics of presently given medical therapies, modified with permission, see Fukagawa et al.²⁰

Name	Administration	
Calcium carbonate	After meals	Ca-containing phosphate binder Tends to cause hypercalcemia during episodes of anorexia Less effective when used with antacids Fewer adverse gastrointestinal reactions than other agents Relatively inexpensive
Sevelamer hydrochloride	Before meals	Calcium-free phosphate binder No intestinal absorption Effective in preventing vascular calcification Effective LDL cholesterol lowering Associated with gastrointestinal side effects, such as constipation and abdominal distension
Lanthanum carbonate	After meals, chewed	Calcium-free phosphate binder Excellent phosphate binding Associated with gastrointestinal side effects, such as nausea and vomiting Intestinal absorption but no evidence of systemic toxicity after long-term administration
Cinacalcet hydrochloride	Once daily, at same time point	Calcimimetic Nadir serum PTH 4–8 h after dosing; nadir serum Ca 8–12 h after dosing To be given at serum Ca levels 9.0 mg/dl Associated with gastrointestinal side effects, such as nausea and vomiting

Abbreviations: LDL, low-density lipoprotein; PTH, parathyroid hormone.
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survival. The long-term treatment policy that advocates ‘parathyroid function should be controlled to avoid the development of hyperparathyroidism’ has been adopted in Japan, and the studies mentioned above support its validity. Increasing the upper limit of the PTH target range could give clinicians the unintended message that it is acceptable for parathyroid function to appear hyperactive as compared with the physiological condition. Furthermore, high PTH levels have been reported to make the control of serum phosphorus/calcium more difficult,³¹ which indirectly disturbs the achievement of therapeutic goals recommended by this guideline.

Taking all the above into account, the JSDT committee decided to conserve in principle the policy proposed by the previous guideline but to widen the target range slightly towards a higher value. Thus, in this revised JSDT clinical practice guideline,¹⁹ the new standard target range for iPTH levels is between 60 and 240 pg/ml.

Severe secondary hyperparathyroidism is defined as iPTH levels > 500 pg/ml or whole, ‘bio-intact’ PTH levels > 300 pg/ml. It also appears reasonable to consider surgical PTx even at lower PTH levels if hyperphosphatemia or hypercalcemia is difficult to manage with medical treatment.

One of the major changes since the release of the previous JSDT guideline is the introduction of cinacalcet hydrochloride to the Japanese market.²⁴ Several studies have shown the

efficacy of cinacalcet for dialysis patients with secondary hyperparathyroidism refractory to treatment with active vitamin D derivatives and those with marked parathyroid hyperplasia, in whom surgical PTx may be the treatment of choice.^{32,33} Indeed, a *post-hoc* analysis of randomized clinical trials reported significant reductions in PTx in patients treated with cinacalcet compared with the placebo plus standard of care group.³⁴ Thus, indications for PTx and cinacalcet treatment overlap significantly. Given the absence of evidence comparing these two treatment modalities, we suggest that the therapeutic decision be made on a case-by-case basis, considering the patient’s preference and general condition. Patients who are refractory to cinacalcet treatment and those who discontinue treatment due to adverse effects should be considered for PTx.

Physicians require clinical evidence to guide the management of severe secondary hyperparathyroidism. Therefore, the Mineral and Bone Disorder Outcomes Study for Japanese CKD Stage 5D Patients (MBD-5D) was conducted. MBD-5D is a 3-year case-cohort study involving hemodialysis patients with severe secondary hyperparathyroidism. The whole cohort was comprised of 8229 patients enrolled in the study, with a sub-cohort of randomly selected patients (3276) from the whole cohort.³⁵ Future studies will investigate the effect of various prescription patterns on clinical outcomes of this patient cohort.

CONCLUSIONS

We have outlined the management strategies for maintaining serum phosphate, calcium, and PTH of Japanese dialysis patients within predefined target ranges, as stated in the new JSDT guideline for CKD-MBD. At present, their number is around 300,000 and their mean age 66.9 years. It is important to assess and take into account the nutrition status of these patients. Malnutrition in elderly dialysis subjects greatly limits the possibility to prescribe phosphorus-restricted diets as they may contribute to increase mortality. In Japan, we also hesitate to indicate surgical parathyroidectomy in elderly patients with severe secondary hyperparathyroidism. However, because in Japanese dialysis patients’ crude mortality rate/year is only 10.1%, it is important to start long-term management of CKD-MBD in elderly patients as early as possible. Although Japanese dialysis patients differ in several aspects from those of other countries, we have included in the new JSDT guideline for CKD-MBD evidence based on reports stemming from countries all over the world and published in English during the past 5 years. In addition, we have also analyzed the JSDT registry database for this purpose and incorporated the results, as appropriate. We hope that the revised Japanese guideline will improve the control of secondary hyperparathyroidism and clinical outcomes in the dialysis patient population of our country.

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DISCLOSURE

KY has received research funds and honoraria from Kyowa Hakko Kirin (a company producing and dealing prescription drugs), Chugai Pharmaceutical (a company producing, dealing, importing and exporting prescription drugs), and Japan Tobacco (a company producing and dealing tobacco, drugs, food, and beverage). KY has also received consulting fees from Japan Tobacco. MT has received research funds and honoraria from Chugai Pharmaceutical, Kyowa Hakko Kirin, Bayer Japan, Fuso (a company producing, dealing, importing and exporting prescription dialysate), Novartis, and Astellas. MF declares having received honoraria as a speaker or an advisor/consultant to Kyowa-Hakko Kirin, Chugai, Bayer Japan, and Astellas. MF has also received consulting fees from Novartis, JT, Abbvie, and grant support from Kyowa-Hakko Kirin.

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