*Therapeutic Apheresis and Dialysis* 12(6):514–525
doi: 10.1111/j.1744-9987.2008.00648.x


# Clinical Practice Guideline for the Management of Secondary Hyperparathyroidism in Chronic Dialysis Patients

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**Key Words:** Chronic kidney disease, Clinical practice guideline, Secondary hyperparathyroidism, Serum calcium, Serum phosphorus, Parathyroid hormone, Ethanol injection, Parathyroidectomy.

The kidney plays an important role in mineral metabolism; thus, in most chronic kidney disease (CKD) patients, various abnormalities of bone and mineral metabolism develop, depending upon the stage of the disease. It has been more widely recognized that deranged mineral metabolism in CKD results not only in bone diseases, but also in a higher risk of mortality, possibly through the development of vascular calcification. Accordingly, instead of the classic term "Renal Osteodystrophy (ROD)," a new term, "CKD-Mineral and Bone Disorders (CKD-MBD)," has recently been proposed as a systemic disorder, with cardiovascular disease, fractures, and mortality as major outcomes (1).

Secondary hyperparathyroidism is one of the most common abnormalities of CKD-MBD. Secretion of parathyroid hormone (PTH) is usually stimulated without appropriate correction of hypocalcemia, hyperphosphatemia, and decreased production of 1,25-dihydroxyvitamin D in CKD patients. In such patients, parathyroid hyperplasia, composed of cells with a decreased density of vitamin D and calcium-sensing receptors, develops over the long term, which leads to resistance to medical therapy and the development of extraosseous calcification. Furthermore, medical therapy itself may worsen hypercalcemia and hyperphosphatemia in advanced cases (2). Thus, it is quite important to prevent the development of parathyroid hyperplasia from the early stages of hyperparathyroidism (3).

The Japanese Society for Dialysis Therapy (JSDT) clinical practice guideline for the management of secondary hyperparathyroidism in chronic dialysis patients was originally published in Japanese in 2006 (4). This article contains the guideline text and footnotes translated into English, and the background, rationales and practical explanations originally written for the English version. Members of the working group for the original version are listed in Appendix 1.

Japanese dialysis patients have unique characteristics that are different from those of American and European patients, including a much lower mortality and longer dialysis duration; in addition, there has been a limited availability of new drugs in Japan (5). Accordingly, in order to establish guidelines for Japanese patients, we screened recent papers and reanalyzed the JSDT database, and tried to set the target range of parameters depending as much as possible upon the best survival rates. As in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF K/DOQI) and other guidelines (6), the Japanese guideline is mainly based

Received July 2008.
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on observational studies and, at best, expert opinion (not on randomized controlled trials).

## CHAPTER 1: ESSENTIAL ROUTINE TESTS AND FREQUENCY OF MEASUREMENTS

I. As routine tests, measure the following variables.[1]
II. Frequency of measurement of serum phosphorus (P) and calcium (Ca)
  1. Measure serum P and Ca at least once to twice a month.
  2. In the event of serum P or Ca showing a deviation or a potential deviation from its target control value,[2] measure it weekly until it is stabilized.
  3. Be sure to use corrected values for patients with hypoalbuminemia (albumin [Alb] < 4 g/dL), according to Payne's equation:

$$\text{Corrected value of Ca (mg/dL)} = \text{Observed value of Ca} + (4 - \text{Alb})$$

III. Frequency of measurement of PTH and a bone metabolism marker
  1. Usually measure PTH once every 3 months; however, during active treatment[3] or after a change of treatment, measure it at least once a month for 3 months until it is stabilized.
  2. As a marker of bone metabolism, use serum alkaline phosphatase (ALP) first, and measure it monthly.

## CHAPTER 2: MANAGEMENT OF SERUM P AND CA LEVELS

I. Target range of serum P and Ca[4]
  1. Target range of serum P
     3.5–6.0 mg/dL
  2. Target range of serum Ca
     8.4–10.0 mg/dL
II. Treatment based on the target range of serum P and Ca (see Fig. 1 and Appendix 2)
  1. Assign a higher priority to maintaining serum P and corrected serum Ca within the target range than to maintaining serum PTH within its target range.
  2. Select the method of treatment by using serum P and corrected serum Ca as indicators.[5]
  3. Change the treatment promptly if serum P ≥ 7.0 mg/dL or corrected serum Ca ≥ 10.5 mg/dL.
  4. Perform dose reduction/discontinuation of active vitamin D and/or calcium carbonate therapy in the event of hypercalcemia, and increase the dose of P adsorbents and reduce the dose or discontinue active vitamin D therapy in the event of hyperphosphatemia.

## CHAPTER 3: CONTROL OF PARATHYROID FUNCTION AND EVALUATION OF BONE METABOLISM

I. Measurement of PTH
  1. PTH is measured as intact PTH (iPTH),[6] as an indicator of parathyroid function.
  2. The status of bone metabolism can be estimated to some extent from the iPTH levels.
II. Target range of PTH
  1. The target range of iPTH should be set at 60–180 pg/mL, which is considered most satisfactory for better survival.[7]
  2. The prerequisite for control of PTH is that the P and Ca levels are adequately controlled.
III. Treatment for deviation of PTH from the target range
  1. If the iPTH levels are much higher than the upper limit of the target range, while serum P and Ca are below the upper limits of the target ranges, decrease PTH by using an active vitamin D preparation.
     a. For this purpose, intravenous use is preferable to oral use.[8]
     b. If serum P and Ca are within the target range, and iPTH is kept within the target range by the treatment listed in (III.1.a), switching to maintenance therapy with an oral active vitamin D preparation or the like may be possible.
  2. If serum P, Ca, and iPTH cannot all be maintained within the target range, even by

[1]Generally use the values obtained at the beginning of the first hemodialysis session in each week.

[2,3]"Potential deviation" and "active treatment" are related to active vitamin D pulse therapy, selective percutaneous ethanol injection therapy (PEIT), and parathyroidectomy (PTX).

[4]The serum Ca × serum P product can usually be kept at an appropriate level by maintaining serum P and corrected serum Ca within the target range.

[5]The dose of calcium carbonate may be increased to 3 g/day.

[6]Measured values of bio-intact PTH or whole PTH, a parameter of 1–84PTH, can be converted to intact PTH values by the following equation: Intact PTH = 1–84PTH × 1.7

[7]Under the present guidelines, priority is given to longer survival, although there is an opinion that the target control value of intact PTH should be higher to maintain bone metabolism.

[8]Pay even closer attention to the control of serum P and Ca during treatment with intravenous preparations of active vitamin D or its analogs.

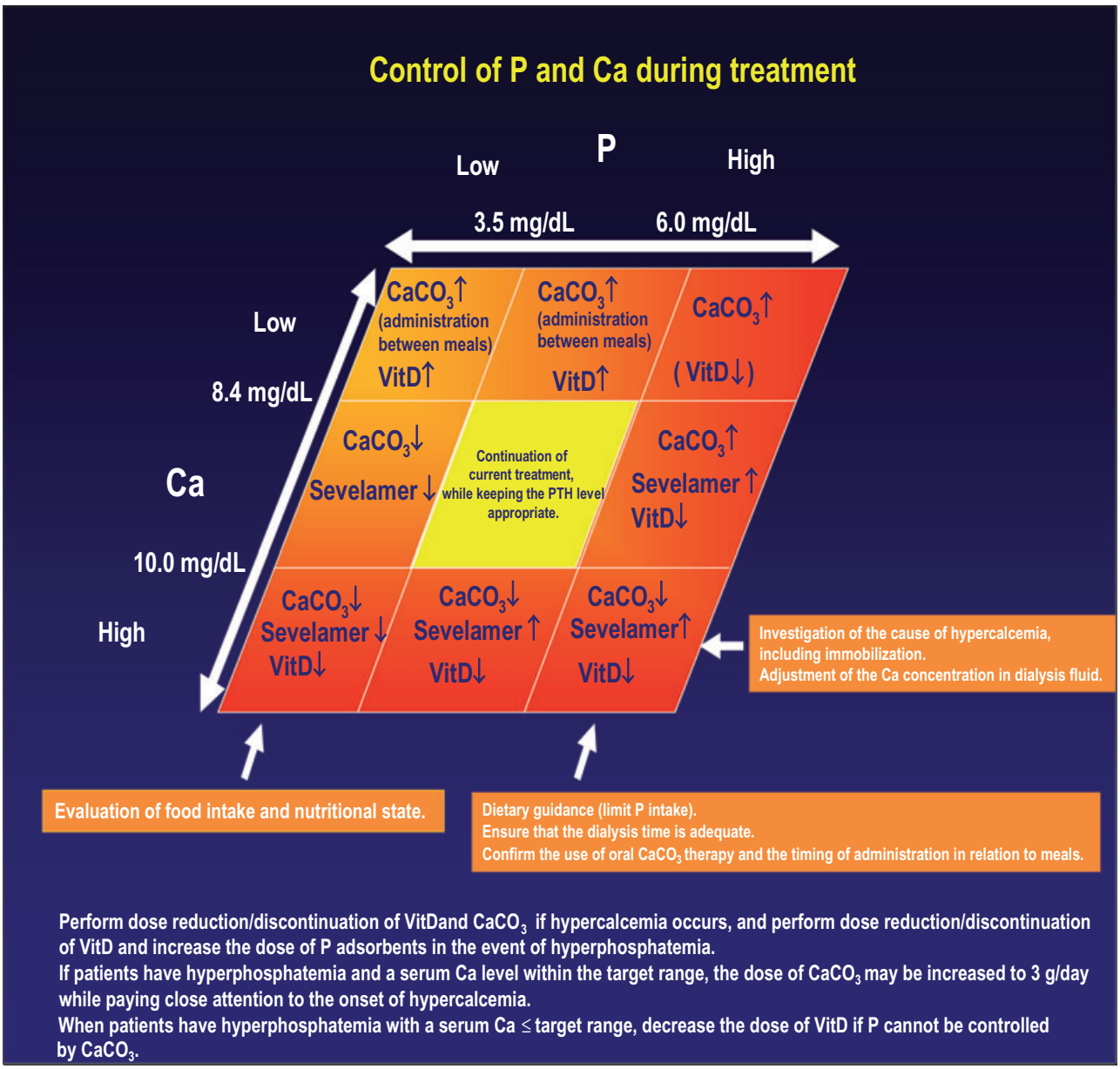


**FIG. 1.** Control of phosphorus (P) and calcium (Ca) during treatment. $CaCO_3$, precipitated calcium carbonate; PTH, parathyroid hormone; Vit D, active vitamin D.

administration of an active vitamin D preparation, consider performing parathyroid intervention.

IV. Evaluation of bone metabolism
   1. Serum ALP is a useful marker of bone metabolism in the absence of complications such as hepatopathy or hematological disorders.[9]
   2. Imaging techniques, including computed tomography (CT), are useful for detecting fractures and ectopic calcification.[10]
   3. Bone biopsy is considered useful in the following cases.
      a. If there is a marked difference between the bone metabolism marker values and the serum P, Ca, and iPTH levels that would be estimated from it.

[9]Measurement of bone metabolism markers, especially bone alkaline phosphatase, is useful for the evaluation of bone turnover.

[10]It has been reported that measurement of the bone salt content or bone mineral density is useful, although still controversial, for predicting the risk of fracture.

b. If osteomalacia is suspected because of a history of heavy exposure to aluminum (Al), iron (Fe), cadmium (Cd), or the like.
c. If a pathologic fracture, bone pain, delayed fracture healing, etc. of unknown etiology occurs.

## CHAPTER 4: INDICATIONS AND METHODS OF PARATHYROID INTERVENTION

I. Parathyroid intervention (parathyroidectomy or percutaneous ethanol injection therapy [PEIT]) should be considered if a high blood PTH level remains resistant to medical treatment,[11] and hypercalcemia (s-Ca > 10.0 mg/dL) or hyperphosphatemia (s-Pi > 6.0 mg/dL) is also noted.[12,13]

## BACKGROUND AND RATIONALE

### Chapter 1

Abnormalities of mineral and bone metabolism in patients with chronic kidney disease (CKD) have traditionally been assessed and managed in terms of renal osteodystrophy (ROD); however, it has been demonstrated that abnormal mineral and bone metabolism in CKD not only produces bone lesions, but also influences the prognosis, most presumably through affecting cardiovascular damage progression over the long-term. Consequently, a new concept of CKD-MBD was introduced (1). This paradigm shift of the disease concept has resulted from research on evidence-based medicine (EBM) principally performed since 1990 and the publication of guidelines based on such research. EBM studies have used survival as the main outcome measure in a large number of cases, and it has become evident that CKD-MBD is deeply involved in the prognosis of dialysis patients. In 2003, the K/DOQI guidelines were released by the National Kidney Foundation (NKF) in the United States. In Japan, guidelines for the treatment of secondary hyperparathyroidism in patients on dialysis (JSDT guidelines) were issued in Japanese in 2006 (4). It should be noted that this JSDT guideline was the first clinical guideline to appear after the clinical concept of CKD-MBD was demonstrated by Kidney Disease: Improving Global Outcomes (KDIGO), and therefore the principle of this clinical guideline basically accords with this paradigm shift.

This clinical guideline has been established for clinical application in Japan, and therefore is suited to the present conditions of Japanese clinical practice. Especially with regard to the assessment of serum phosphorus levels, we must consider the timing of blood sampling for measurements. In the USA, blood is frequently collected 2 days after dialysis, but in Japan collection generally occurs 3 days after dialysis. To use this guideline, serum Ca levels must be corrected by serum albumin levels with Payne's equation, because the main evidence applied in this guideline was based on albumin-corrected Ca levels. No definite evidence has been obtained to establish the appropriate frequency of each laboratory examination, but the upper limit is practically limited by economical reasons.

The present guideline is to be reconsidered whenever new evidence and/or therapeutic methods appear in future.

### Chapter 2

*Management of serum phosphate levels*

The JSDT guideline was drafted on the basis that PTH should be controlled with the serum phosphorus and calcium levels remaining under optimal control. Under these circumstances, the regulation of PTH is limited by the range of target values for serum phosphorus and calcium.

The target values in the K/DOQI guidelines were determined based on the results of a large-scale retrospective study (6–8). Since then, several other large-scale studies have been carried out (9,10) and have confirmed the validity of the K/DOQI guidelines. Since the prognosis of Japanese dialysis patients differs somewhat from that in other countries (11), it was necessary to analyze outcomes over a longer period among Japanese patients (12).

A longitudinal study with this objective was conducted in Japanese patients. Data on 27 404 patients treated between 2000 and 2003 were extracted from the database of the Japanese Society for Dialysis Therapy and analyzed. According to the report by Nakai et al. summarizing the results (12), when the risk of death over 3 years was set at 1.0 for patients with a serum phosphorus level of 4.0–4.9, the risk increased gradually, but significantly, with an increase of serum phosphorus, being 1.105 at 5–6 mg/dL, 1.172 at 6–7 mg/dL, 1.425 at 7–8 mg/dL, 1.893 at 8–9 mg/dL, and 1.985 at >9 mg/dL.

[11] If the upper limit of the target range for PTH is exceeded despite medical treatment, parathyroid intervention should be taken into consideration. It is strongly recommended if iPTH > 500 pg/mL.

[12] The possibility of nodular hyperplasia is high if the volume or longer diameter estimated by ultrasonography is ≥500 $mm^3$ or ≥1 cm, respectively. These are important factors for selecting parathyroid intervention.

[13] If only one gland shows enlargement, with an estimated volume ≥500 $mm^3$ or an estimated longer diameter ≥1 cm, and this gland can be targeted, it may be possible to control hyperparathyroidism for a long period by performing PEIT.

With regard to the lower limit of phosphorus, several authors have reported that the prognosis becomes worse at ≤4 mg/mL or 3 mg/mL (8,9), but Nakai et al. found no relationship between the three-year survival rate and hypophosphatemia (12). These results are similar to those of a large-scale study involving 14 829 patients (USRDS) (10). To avoid the risk of postdialysis hypophosphatemia, the lower limit of phosphorus was set at the lower limit of the normal range (3.5 mg/dL) of healthy subjects as the lower target value.

As mentioned in the previous chapter, it is necessary to take into consideration the timing of measurement in Japan. To assess the influence of the timing of measurement, serum phosphorus was measured in the same patients at 2 days after hemodialysis, and also at 3 days after hemodialysis (11,13). Among patients in whom the serum phosphorus levels were ≥5.6 mg/dL (6.73 ± 1.46 mg/dL) at 3 days after hemodialysis, the levels at 2 days after dialysis were significantly decreased to 5.41 ± 1.36 mg/dL ($P < 0.001$) (11). Considering that blood collected after 3 days is measured in Japan, the level of 5.5 mg/dL or more in the K/DOQI is considered to correspond to 6.0 mg/dL or more, so the target value for phosphorus can be considered as equivalent between the K/DOQI and JSDT guidelines. Although 4.6 mg/dL is set as the upper limit in Europe, the target value was determined from measured data to achieve the best prognosis, because serum phosphorus levels decrease considerably after hemodialysis.

As the target value for phosphorus has been based on the results of longitudinal studies, mostly utilizing only baseline values, it would be desirable to assess the influence of the laboratory values over time on the prognosis. Recently, Kalantar-Zadeh et al. measured the serum phosphorus concentrations every 3 months in 58 058 patients on maintenance dialysis for 2 years (from 2001 to 2003), and reported that time-dependent Cox models with repeated measures show that serum phosphorus levels associated with the lowest relative risk of death were 5.0–5.99 mg/dL. In their investigation, the results of time-dependent Cox models showed a greater influence of hyperphosphatemia on the prognosis than was revealed by fixed-covariate Cox models of only the baseline values (14). These results support the suitability of setting 6.0 mg/dL as the upper limit of the target range in the JSDT guidelines and indicates that the relative risk of an adverse outcome is increased when hyperphosphatemia remains untreated.

Noordzij et al. have confirmed that levels were within the control target value of K/DOQI in 1629 incident dialysis patients (including 1043 hemodialysis patients) every six months, and demonstrated that the risk of death is decreased when levels remain within the target range (15). Rodriguez-Benot et al. performed a prospective study in 385 patients over 10 years and concluded that mild hyperphosphatemia (5.01–6.5 mg/dL) is an independent risk factor for death in patients on dialysis (16).

Kalantar-Zadeh et al. recently demonstrated that patients with both falls and rises in serum phosphate from the baseline value at two years exhibited a significant increase in mortality (14). This result suggests that not only serum phosphate levels, but also the nutritional status of each individual patient must be taken into account in evaluating serum phosphate levels in dialysis patients. Serum P levels of more than 6.0 mg/dL are also associated with the refractoriness of hyperactivated parathyroid function to active vitamin D therapy (17).

*Management of serum calcium levels*

Since serum calcium levels are not decreased after a dialysis session, the target range of serum calcium is determined according to: (i) the calcium concentrations that are preferable to patient survival; and (ii) the normal range of healthy subjects. According to the report by Nakai et al. (12), which analyzed Patient Registration of the Japanese Society for Dialysis Therapy, there is a significantly higher mortality risk at three years when baseline serum calcium levels are ≥10.0 mg/dL. The hazard ratio for serum calcium between 10.0 and 10.9 mg/dL was 1.098 (95% confidence interval 1.020–1.182, $P = 0.0129$) when the reference serum calcium was set at 9.0–9.9 mg/dL. Although some cohort studies have shown that patient survival is better with lower serum calcium levels (9–11), Nakai's analysis in Japan could not show better survival when serum calcium was lower than the target range.

Recently, Kalantar-Zadeh et al.'s study, in which time-dependent Cox analysis was performed (14), also confirmed the pertinence of target calcium levels of the K/DOQI guideline and the present guideline; however, Noordzij et al. (15), who performed prospective time-dependent survival analysis of 1629 incident dialysis patients (including 1043 hemodialysis patients) to examine the validity of the K/DOQI guideline, reported no significant improvement of survival even when serum calcium was controlled within the target range of the K/DOQI guideline. Further prospective, long-term studies enrolling a large number of patients are needed to establish the target range of calcium considering better survival of dialysis patients.

In the present guideline, unallowable levels of serum calcium are indicated, as well as the target range of calcium. If the corrected serum calcium exceeds 10.5 mg/dL, the guideline recommends "Changing the treatment promptly." As for the dose of calcium carbonate as a phosphate binder, the guideline states that "the dose of oral calcium carbonate should not exceed 3.0 g/day," since it is reported that calcium overload significantly affects vascular calcification in dialysis patients (18,19); however, since sevelamer hydrochloride frequently causes gastrointestinal symptoms such as constipation in Japanese patients, and since sevelamer decreases serum phosphate less potently than calcium carbonate, sevelamer hydrochloride would be used together with calcium carbonate. The combination therapy with calcium carbonate and sevelamer hydrochloride were demonstrated to be better tolerated and showed higher compliance than calcium carbonate or sevelamer hydrochloride monotherapy (20).

## Chapter 3

*Assessment of parathyroid function*

Circulating parathyroid hormone levels are indicative of parathyroid activity. For this purpose, an iPTH assay system has most frequently been applied in CKD patients. Since our present understanding of secondary hyperparathyroidism in CKD patients is largely dependent on the accumulation of data from iPTH measurement, this guideline regards this assay system as the standard method to assess parathyroid function; however, another assay system that specifically detects 1–84 PTH molecules, which is referred as "the 3rd generation PTH assay," has been developed, and has recently become available in clinical practice (21). In cross-sectional studies, the results of these two assays show a tight correlation with the correlation coefficient number of 1.7 (22–26). Thus, the 3rd generation PTH assay levels can be converted to iPTH levels by multiplying them by 1.7. The reason that this conversion formula appears in this guideline is to promote the application of the 3rd generation PTH assay at the bedside, by guaranteeing its continuity from the conventional iPTH assay.

In cross-sectional studies, iPTH levels correlate with bone turnover estimated by bone histomorphometry or bone metabolic markers in CKD patients (27–31). Therefore, circulating PTH levels are now considered as the most reliable non-invasive bone turnover marker, as well as a marker of parathyroid activity; however, it is not accurate enough to specify bone turnover merely by itself. The gold standard for assessing bone metabolism is bone histomorphometry (32).

There is no established consensus on the determination of "optimal parathyroid function in dialysis patients." For serum P or Ca levels, it has been widely accepted that standard levels be set based on the relationships between these levels and life prognosis (6). As for circulating PTH levels, however, this approach has somehow not been applied. Instead, "optimal parathyroid function" has been considered to be "the parathyroid function that would maintain bone turnover similar to that with a normal kidney function." In CKD patients generally, more activated parathyroid function is required than with normal kidney function in order to maintain bone turnover similar to standard levels. As such, approximately 2–3 times greater circulating PTH levels than the standard levels in those with normal kidney function have been recommended for dialysis patients (33,34).

However, it has not yet been proved that bone turnover similar to that in those with normal kidney function is beneficial with regard to life prognosis and/or maintenance of daily life activity in dialysis patients (35–37). On the other hand, the safety of a prolonged mild hyperparathyroid condition also has not been confirmed. Therefore, a "bone metabolic condition similar to that in those with normal kidney function" is merely a surrogate outcome at present that may not be "the outcome that all dialysis patients should aim at." Thus, in this guideline, "optimal parathyroid function in dialysis patients" is not determined by its relation to bone turnover, but defined as "the PTH levels that are advantageous for better life prognosis," such as in those cases with Ca and P.

According to the recently reported three-year longitudinal study by the JSDT, the mortality risk was not greatly (but was significantly) lower in the group of patients with iPTH levels < 120 pg/mL than in the standard group set at 180 pg/mL < iPTH < 360 pg/mL (12). Based on this finding, and taking practical conveniences into consideration, this guideline set 60 pg/mL < iPTH < 180 pg/mL as the optimal iPTH levels in chronic dialysis patients. Reconsideration of this PTH management strategy may be required after the future accumulation of evidence regarding outcomes other than life prognosis, such as the risk of fracture or parathyroid intervention.

Because the contribution of circulating P or Ca levels to life prognoses seems to be more significant than that to parathyroid function (9), they must be

maintained within the standard levels appearing in the earlier chapters before trying to control iPTH levels.

*Medical treatment for secondary hyperparathyroidism*

Therapy with active vitamin D agents is applied when parathyroid function greatly exceeds standard levels (38,39). Active vitamin D therapy demonstrates calcemic action and often phosphatemic action as well (40). Therefore, more attention should be paid to its safety than to its efficacy during active vitamin D therapy, since P/Ca control is more important than parathyroid control. Supportive therapies, including the application of non-Ca containing oral phosphate binders (41,42), diet, and dialysate containing 2.5 mEq/L (43,44) of Ca may be helpful for safer active vitamin D therapy; however, there has been no evidence provided indicating that the application of these supportive therapies would provide better life prognosis in dialysis patients.

Active vitamin D therapy is judged to be successful only when circulating P, Ca, and PTH levels are simultaneously maintained within the target ranges. Aimless continuation of active vitamin D treatment should be avoided in those cases with secondary hyperparathyroidism refractory to medical therapies (45), and parathyroid intervention therapy should be considered instead. It is sometimes useful to predict the long-term efficacy of active vitamin D agents before (46–48) or during (17) therapy. Ultrasonographic parathyroid examination is often applied for this purpose (49,50).

*Assessment of bone metabolism*

Bone biopsy is considered to be the "gold standard" in the diagnosis of metabolic bone diseases (32); however, it is difficult to perform it regularly because of its invasiveness. Since bone turnover fluctuates in monthly order, bone biopsy is generally not a suitable method for determining the treatment strategy in daily clinical practice. Bone-specific alkaline phosphatase activity helps in estimating bone turnover in CKD patients (51). For this purpose, even non-specific alkaline phosphatase activity could be useful in those without liver or blood disorders. It remains controversial whether bone mineral densitometry can successfully predict the bone fracture risk in dialysis patients (52–56). Bone strength is determined by bone mass and bone quality. Since the spectrum of bone quality seems to be quite widely distributed in dialysis patients, the relative importance of bone mass in determining bone strength may be limited. Taken together, there is no routinely available standard method to evaluate bone metabolism in dialysis patients at present.

As mentioned above, bone biopsy is not a suitable method to be carried out routinely in daily clinical practice. Nevertheless, it is strongly recommended that it be performed in those suffering from bone metabolic disorders of unknown etiology. Bone biopsy is the "gold standard" in the diagnosis of metabolic bone diseases, and a precise diagnosis often provides an appropriate treatment strategy.

## Chapter 4

*Parathyroid intervention therapy*

Hyperparathyroidism is a common complication in hemodialysis patients that is associated with mortality (57,58). Patients with severe secondary hyperparathyroidism suffer from several clinical symptoms; that is, bone and joint pain, muscle weakness, irritability, itching, bone loss, anemia resistant to erythropoietin, dilated cardiomyopathy (DCM), calciphylaxis, and so on. While in the majority of patients secondary hyperparathyroidism can be controlled by medical treatment, this treatment does not always provide adequate control of secondary hyperparathyroidism. Some patients require parathyroid intervention therapy, including parathyroidectomy (PTx) and PEIT. Successful surgical treatment results in a dramatic drop in PTH levels, relief from some clinical symptoms, and a reduction in mortality (57–66).

*Indications of parathyroid intervention therapy*

Among patients with CKD, high P, high Ca, and high PTH levels are associated with mortality, primarily due to cardiovascular complications induced by ectopic calcifications. When serum P, Ca, and PTH levels cannot be maintained within the target range, medical treatment including active vitamin D therapy should not be continued and parathyroid intervention therapy should be considered to avoid progression of ectopic calcification. Parathyroid intervention therapy should be recommended in patients with severe hyperparathyroidism (persistent high serum levels of iPTH levels > 500 pg/mL), associated with hyperphosphatemia (serum P > 6.0 mg/dL) and/or hypercalcemia (serum Ca > 10.0 mg/dL) that is refractory to medical therapy. Moreover, if patients suffer from the clinical symptoms mentioned above, parathyroid intervention therapy is absolutely indicated.

Assessment of any parathyroid masses with ultrasonography is an important factor in predicting the

response to medical treatment and to making decisions regarding surgical treatment (49,50,67–69). In CKD patients, parathyroid glands initially grow diffusely and polyclonally, and then are transformed into nodular hyperplasia with several nodules in which parathyroid cells proliferate monoclonally and with high growth potential (70,71). Moreover, parathyroid cells consisting of nodules have decreased their expression of vitamin D receptors and calcium sensing receptors (72,73). These findings indicate that nodular hyperplasia may be resistant to medical treatment. Based on examination of removed parathyroid glands at surgery, more than 85% of glands weighing >500 mg are nodular hyperplastic glands (74). The volume of parathyroid glands can be estimated by ultrasonography, and glands for which the volume exceeds 500 $mm^3$, or the largest diameter exceeds 1 cm, are possibly showing signs of nodular hyperplasia (49,74). The total glandular weight, which is measured at surgery, has a good correlation with preoperative PTH levels in patients undergoing PTx. Concerning the relationship, 2000 mg of total glandular weight corresponds to iPTH levels of 500 pg/mL. Then, if the iPTH levels exceed 500 pg/mL, the patient may have at least one nodular hyperplastic gland (75).

*Surgical procedures*

PEIT is widely accepted as a treatment for advanced secondary hyperparathyroidism in Japan (76–79). Concerning long-term outcomes, secondary hyperparathyroidism can be managed over the long-term by PEIT when only one parathyroid gland is enlarged to more than 500 $mm^3$, as estimated by ultrasonography (80). After PEIT, it is difficult for PTx to identify parathyroid tissue and the recurrent laryngeal nerve. PEIT should therefore be limited to patients in whom only one gland is substantially enlarged and also both PEIT and PTx should be performed by skilled operators.

There are many variations on the procedure to accomplish PTx, which include subtotal PTx, total PTx with autograft, and total PTx without autograft. Subtotal PTx and total PTx with autograft are widely accepted for secondary hyperparathyroidism; however, there are no significant differences regarding the efficacy and recurrence rate between the two operative procedures (65,81). For patients who require long-term hemodialysis after PTx, the risk or recurrence is not negligible (approximately 20% at the 10th year after PTx) (60,61). Because it is easier and safer to remove the residual parathyroid tissue from the forearm at recurrence compared to neck re-exploration, total PTx with forearm autograft is recommended in a patient who has to continue hemodialysis for long periods after the operation. This procedure is chosen for secondary hyperparathyroidism in 90% of institutes in Japan. Total PTx without autograft may not suitable for patients who will receive a kidney transplant, since the control of serum Ca levels may be difficult following kidney transplantation, and the procedure is not recommended because it has not been confirmed that hypoparathyroidism is not harmful in patients undergoing long-term hemodialysis.

*Parathyroid imaging*

The necessity for preoperative parathyroid imaging for re-operation is well-accepted; however, at the initial PTx, some parathyroid surgeons do not feel that it is necessary. The guideline recommends performing preoperative imaging before even the initial PTx because missed parathyroid glands are responsible for persistent hyperparathyroidism and recurrence (61). Ectopic parathyroid glands, such as in thymic tissue, and mediastinal, intrathyroidal, undescended and supernumerary glands may be pitfalls to detecting all parathyroid glands (82–85). A combination of neck ultrasound or CT and scintigram ($^{201}$TlCl and $^{99m}$TC $O^{4-}$ subtraction or $^{99m}$Tc MIBI) can almost cover detection of these ectopic glands (86,87).

*Calcium replacement therapy*

After successful PTx, serum Ca levels will drop rapidly and Ca supplementation is required. In patients with severe high turnover bone loss (hungry bone disease), intravenous Ca replacement therapy from a central venous line is recommended (88). Medical treatment, controlling serum P, Ca, and PTH levels within the target range after PTx is important to prevent recurrent hyperparathyroidism and obtain a good survival rate.

## CONCLUSION

The current JSDT guideline has been mainly based on the available data for Japanese dialysis patients, most of which were observational studies. Verification of the appropriateness of the guideline and further studies are mandatory for potential revision.

This guideline did not include other abnormalities of CKD-MBD, such as vascular calcification and amyloidosis. Neither did it refer to several important issues such as the role of vitamin D therapy on survival (89,90). Furthermore, new therapeutic modalities including cinacalcet (91), have recently been introduced into the Japanese market, after the origi-

nal version of guideline was published. Thus, a revised version of the guideline should be prepared in the near future.

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## APPENDIX 1

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## APPENDIX 2

**Classifying the serum levels of P and Ca**

Classify the serum levels of P and Ca using the following nine patterns to select the appropriate treatment.

1. Serum P ≥ target range
   Give dietary guidance to limit the intake of P and to ensure that the dialysis time is sufficient, irrespective of the serum Ca level. Then select the appropriate treatment for hyperphosphatemia based on the serum Ca levels.
   <u>High serum Ca</u>
   Confirm that calcium carbonate is being taken orally during meals or immediately afterward.
   Dose reduction or discontinuation of calcium carbonate (switch to sevelamer hydrochloride).
   Reduce the dose or discontinue active vitamin D.
   Investigation of the cause of hypercalcemia, including immobilization.
   Adjustment of the Ca concentrations in dialysis fluid.
   <u>Serum Ca within the target range</u>
   Confirm that calcium carbonate is being taken orally during meals or immediately afterward.
   Commence treatment with or increase the dose of calcium carbonate/sevelamer hydrochloride.
   Reduce the dose or discontinue active vitamin D.
   <u>Low serum Ca</u>
   Confirm whether oral calcium carbonate is actually being taken.
   Commence treatment with or increase the dose of calcium carbonate.
   Reduce the dose of active vitamin D if P is not controlled by increasing the dose of calcium carbonate.
2. Serum P within the target range
   <u>High serum Ca</u>
   Dose reduction or discontinuation of calcium carbonate (switch to sevelamer hydrochloride).

Reduce the dose or discontinue active vitamin D.
Investigation of the cause of hypercalcemia, including immobilization.
Adjustment of the Ca concentrations in dialysis fluid.
Serum Ca within the target range
Continue the current treatment (while trying to maintain appropriate PTH levels).
Low serum Ca
Commence treatment with or increase the dose of calcium carbonate (administration between meals).
Commence treatment with or increase the dose of active vitamin D.

3. Serum P ≤ target range
Confirm whether food intake is sufficient and whether or not the nutritional state is poor, irrespective of the serum Ca levels. Then select the appropriate treatment for hypophosphatemia based on the serum Ca levels.
High serum Ca
Reduce the dose or discontinue calcium carbonate/sevelamer hydrochloride.
Reduce the dose or discontinue active vitamin D.
Investigation of the cause of hypercalcemia, including immobilization.
Adjustment of the Ca concentrations in the dialysis fluid.
Serum Ca within the target range
Reduce the dose or discontinue calcium carbonate/sevelamer hydrochloride.
Low serum Ca
Commence treatment with or increase the dose of calcium carbonate (administration between meals).
Commence treatment with or increase the dose of active vitamin D.

## APPENDIX 3

Maintexts and footnotes of this guidline can be downloaded from JSDT homepage in English: http://www.jsdt.or.jp/index_e.html