

## Clinical significance of parathyroid intervention on CKD-MBD management

Hiroaki Ogata<sup>1</sup>, Masahide Mizobuchi<sup>1,2</sup>, Fumihiko Koiwa<sup>3</sup>, Eriko Kinugasa<sup>1</sup> and Tadao Akizawa<sup>2</sup>

<sup>1</sup>Department of Internal Medicine, Showa University Northern Yokohama Hospital, Yokohama, <sup>2</sup>Department of Nephrology, Showa University School of Medicine, Tokyo and <sup>3</sup>Division of Nephrology, Department of Internal Medicine, Showa University Fujigaoka Hospital, Yokohama, Japan

### Abstract

Recently published ‘Guidelines for the management of secondary hyperparathyroidism in chronic dialysis patients’ by the Japanese Society for Dialysis Therapy advocate that percutaneous ethanol injection into enlarged glands, which has been considered as the only alternative to parathyroidectomy (PTx), should be indicated in patients with a single enlarged parathyroid gland (estimated volume >500 mm<sup>3</sup>, or estimated major axis >10 mm), and that PTx should be recommended in patients with multiple enlarged glands. Cinacalcet cannot achieve optimal control of chronic kidney disease–mineral bone disorder in all patients, and parathyroid intervention will be required in a considerable number of patients with refractory secondary hyperparathyroidism.

### Clinical significance of CKD-MBD

Chronic kidney disease (CKD) is inevitably associated with various disruptions in bone mineral metabolism, including abnormalities in the concentrations of serum calcium (Ca), phosphate (P) and parathyroid hormone (PTH), as well as 1,25(OH)<sub>2</sub> dihydroxy-vitamin D<sub>3</sub> deficiency, as the residual kidney function declines [1,2]. It has become evident that various bone mineral disorders associated with CKD (CKD-MBD) are also associated with the development of cardiovascular disease. Therefore, recently published guidelines, namely ‘the Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical guidelines for bone metabolism and disease in CKD’ [3] and ‘Guidelines for the management of secondary hyperparathyroidism in chronic dialysis patients’ [4,5] by the Japanese Society for Dialysis Therapy (JSDT), have set stringent targets for the concentrations of serum Ca and P (Table 1). Nationwide surveys, which are carried out annually, have demonstrated that poor Ca and P management, as well as abnormal PTH concen-

tration, are associated with high morbidity and mortality in Japanese patients on haemodialysis [6,7]. Observational studies have also shown that hyperphosphataemia, hypercalcaemia and increased Ca × P product are more strongly associated with high cardiovascular morbidity and mortality than elevated PTH level [8,9]. The JSDT guidelines recommend the management of P and Ca concentrations prior to controlling the PTH concentration in patients with secondary hyperparathyroidism (SHPT). However, SHPT is highly prevalent in long-term dialysis patients, and excess PTH has been demonstrated to be one of the uraemic toxins [1,8–12]. A markedly high PTH concentration is implicated in various complications, including hypertension, abnormal lipid metabolism, glucose intolerance, erythropoietin-resistant anaemia and abnormal cardiovascular remodelling in uraemia [1,8–12]. In fact, parathyroidectomy (PTx) has been shown to ameliorate these abnormalities in patients with severe SHPT. In addition, PTx was reported to reduce the fracture risk and long-term mortality rate in dialysis patients [13,14]. Calcimimetics treatment, which can be considered as a pharmacological parathyroid ablation, has been demonstrated to improve cardiac and renal remodelling in uraemic rats [12,15]. Thus, it is of clinical importance to control the serum PTH concentration, as well as the serum P and Ca concentrations in uraemic patients.

### Limitation of conservative treatment and indication for parathyroid intervention

Although clinical guidelines recommend the strict management of CKD-MBD on the basis of clinical evidence, many patients have not satisfied the guideline targets. A large observational study showed that only 21% of the patients satisfied the K/DOQI guidelines’ criteria for PTH concentration and 5% met the combined targets for Ca, P, Ca × P product and PTH under conventional treatment [16]. The parathyroid cells within nodular hyperplastic lesions are more proliferative than those within diffuse hyperplastic lesions, and express less vitamin D receptor (VDR) and calcium sensing receptor (CaSR) [17–19]. Consequently,

Correspondence and offprint requests to: Hiroaki Ogata, Department of Internal Medicine, Showa University Northern Yokohama Hospital, Chigasaki-chuo 35-1, Tsuzuki, Yokohama 224-8503, Japan. Tel: +81-45-949-7000; Fax: +81-45-949-7927; E-mail: ogatah@med.showa-u.ac.jp

**Table 1.** Clinical guidelines for CKD-MBD and parathyroid intervention [3,4]

	K/DOQI (2003)	JSDT (2006)
Target levels		
Phosphate	3.5–5.5 mg/dL (1.13–1.78 mmol/L)	3.5–6.0 mg/dL
Calcium	8.4–9.5 mg/dL* (2.10–2.37 mmol/L)	8.4–10.0 mg/dL*
Ca × P product	<55 mg <sup>2</sup> /dL <sup>2</sup>	–
Intact PTH	150–300 pg/mL (16.5–33.0 pmol/L)	60–180 pg/mL
Indication for parathyroid intervention	iPTH > 800 pg/mL (88.0 pmol/L) +Hypercalcaemia (>10.2 mg/dL*) +Hyperphosphataemia (>6.0 mg/dL) Calciophylaxis (iPTH >500 pg/mL)	Elevated PTH refractory to medical treatment (iPTH > 500 pg/mL) +Hyperphosphataemia (>6.0 mg/dL) +Hypercalcaemia* (>10.0 mg/dL) Persistent clinical symptoms Bone/muscle pain Severe pruritus Calciophylaxis Progressive osteopenia Ectopic soft tissue calcification ESA-resistant anaemia DCM-like heart PTG >500 m <sup>3</sup> or 10 mm in diameter

iPTH, intact parathyroid hormone; PTG, parathyroid gland; ESA, erythropoiesis-stimulating agent; DCM, dilated cardiomyopathy.

\*Adjusted calcium concentration.

when at least one parathyroid gland progresses to nodular hyperplasia, SHPT cannot be treated even with injectable calcitriol or its analogues. Tominaga *et al.* have reported that over 85% of resected parathyroid glands from dialysis patients with severe SHPT had nodular hyperplastic lesions pathologically when the glandular weight was more than 500 mg [20]. In fact, an enlarged parathyroid gland, with an estimated volume of over 500 mm<sup>3</sup> or major axis of >10 mm as determined by ultrasonography, might be predictive of poor responsiveness to conventional medical treatment, even by administration of intravenous active vitamin D analogues [4,21,22].

When SHPT does not respond to medical treatment, parathyroid intervention should be indicated. Parathyroid intervention can be divided into two major categories: PTx and percutaneous ethanol injection into enlarged parathyroid glands (PEIT) [1,3,4,12,23–25]. Parathyroid intervention is very effective in reducing the PTH level without increasing the Ca and P loads in patients with SHPT. It can be expected to markedly improve both P and Ca management, particularly when PTx is successfully performed in patients with severe SHPT [12,14,25–27]. PEIT has been carried out as a less invasive alternative to PTx for refractory SHPT [1,3,4,12,22–24,28,29]. PEIT, as well as PTx, reduces serum PTH levels rapidly when the enlarged PTG is adequately destroyed.

In addition, more recently, the direct injection of active vitamin D analogues has also been performed in Japan [1,4,12]. Repeated vitamin D injections into enlarged parathyroid glands were reported to be effective in suppressing PTH secretion without the risk of recurrent nerve paralysis, which is one of the complications associated with PEIT [4]. The induction of parathyroid cell apoptosis and upregulation of VDR expression by parathyroid cells upon exposure to extremely high vitamin D concentrations have been shown to be one of the mechanisms underlying the decrease in size of the parathyroid glands [30]. These results suggest that percutaneous direct injection therapy may

be considered a powerful therapeutic tool for refractory SHPT.

### Parathyroid intervention in clinical guidelines for CKD-MBD

Table 1 summarizes the target values for P, Ca and PTH and the indication for parathyroid intervention in the K/DOQI and JSDT clinical guidelines [3–5]. The indication for parathyroid intervention still remains to be confirmed since there are no studies that define the absolute biochemical and clinical criteria for parathyroid intervention. There is no distinct difference in the indication for parathyroid intervention between the two guidelines. The K/DOQI and JSDT guidelines propose an interim indication for parathyroid intervention in patients refractory to medical treatment with high iPTH levels (>800 in the K/DOQI and >500 pg/mL in the JSDT), associated with hyperphosphataemia or/and hypercalcaemia. Unlike with the K/DOQI guidelines, the JSDT guidelines encourage parathyroid intervention in patients refractory to medical treatment with SHPT-associated complications. The indication for parathyroid intervention proposed by the JSDT guidelines is categorized into three grades: absolute, strongly recommended and considerable indication. Even if the iPTH level does not exceed 500 pg/mL but hyperphosphataemia and/or hypercalcaemia are refractory to medical management, parathyroid intervention is recommended in the JSDT guidelines (Table 2). In addition, the JSDT guidelines propose parathyroid intervention for patients with clinical manifestations associated with refractory SHPT, including musculoskeletal symptoms, severe pruritus, progressive osteopenia, ectopic calcification, erythropoietin-resistant anaemia or dilated cardiomyopathy [4]. Cardiovascular calcification is associated with a higher risk of cardiovascular morbidity and mortality in long-term dialysis patients and is considered to be an

**Table 2.** Indication for parathyroid intervention in dialysis patients with secondary hyperparathyroidism from the JSDT guidelines (modified from reference [4])

Absolute indication (1 and at least one of the following symptoms and signs)	
1	Persistent elevated levels of intact PTH (> 500 pg/mL) with hyperphosphataemia (>6.0 mg/dL) and/or hypercalcaemia (> 10.0 mg/dL), which are refractory to medical therapy
2	(1) Clinical symptoms: musculoskeletal pain, muscle weakness, irritability, insomnia, pruritus, etc. (2) High turnover bone (3) Progressive bone loss (4) Progressive ectopic calcification (5) Calciphylaxis (6) ESA-resistant anaemia (7) Dilated cardiomyopathy-like cardiac involvement
Strongly recommended	
1	Persistent elevated levels of intact PTH (> 500 pg/mL) with hyperphosphataemia (>6.0 mg/dL) and/or hypercalcaemia (> 10.0 mg/dL), which are refractory to medical therapy
2	Persistent elevated levels of intact PTH ( $\leq$ 500 pg/mL) with hyperphosphataemia (>6.0 mg/dL) and/or hypercalcaemia (> 10.0 mg/dL), which are refractory to medical therapy
3	2 and detection of enlarged parathyroid glands by ultrasonography (estimated glandular volume $\geq$ 0.5 cm <sup>3</sup> and/or major axis $\geq$ 10 mm)
Considerable	
	Persistent elevated levels of intact PTH ( $\leq$ 500 pg/mL) with hyperphosphataemia (>6.0 mg/dL) and/or hypercalcaemia (> 10.0 mg/dL), which are refractory to medical therapy

PTH, parathyroid hormone; ESA, erythropoiesis-stimulating agent.

important manifestation of CKD-MBD. When cardiovascular calcification progressively accelerates, parathyroid intervention should be considerable even in patients with mild-to-moderate SHPT in accordance with the JSDT guidelines.

As discussed previously, the volume of the parathyroid gland is a useful maker for predicting the responsiveness to active vitamin D therapy. When the volume of one of the parathyroid glands exceeds 500 mm<sup>3</sup> or 10 mm in the major axis as determined by ultrasonography, parathyroid intervention is also recommended in the JSDT guidelines.

There is a distinct difference in terms of interventional procedure between the two guidelines. In the K/DOQI guidelines, PTx, including subtotal PTx and total PTx with autotransplantation, is primarily recommended as an effective surgical intervention. In contrast, the JSDT guidelines recommend not only PTx, but also PEIT as the primary procedure of parathyroid intervention. The JSDT guidelines advocate that PEIT is expected to reduce iPTH effectively and to manage CKD-MBD for a long period in patients with no more than one enlarged parathyroid gland (> 500 mm<sup>3</sup>) [4,24,28]. In patients with multiple suspected nodular hyperplastic glands, even if PEIT is performed for all targeted glands, the long-term clinical results are unfavourable [23,24,28,29,32]. In addition, the risk of complications, including haemorrhage, recurrent nerve palsy and adhesion to surrounding tissue, increases with the number of injections [24,28]. PTx should be considered in patients with more than two enlarged glands. In patients with calciphylaxis with elevated PTH levels, PTx should be strongly recommended because calciphylaxis is a very emergent complication in uraemic patients [3,4,31].

While PTx removes all parathyroid glands regardless of their size or histology, PEIT selectively destroys only the largest one. Thus, it is very important to control the growth of any residual parathyroid glands, which are presumably responsive to active vitamin D analogues, and to suppress

PTH secretion with medical management, mainly by active vitamin D therapy, after successful PEIT [23,24,28,29]. Otherwise, other glands will consecutively become nodular hyperplastic.

### Parathyroid intervention in the cinacalcet era

It is of considerable interest whether cinacalcet, which has recently become clinically available in Japan, can sufficiently suppress PTH secretion in patients with enlarged parathyroid glands, which are presumably refractory to vitamin D. Cinacalcet significantly reduces the PTH concentration in dialysis patients with SHPT, and simultaneously has favourable effects on Ca and P metabolism, presumably as a consequence of the reduced PTH-driven Ca and P efflux from the bone [33–35]. In fact, cinacalcet has been demonstrated to improve the achievement ratio of the target values stipulated in the K/DOQI guidelines as compared with conventional treatment alone, active vitamin D analogues and P binders in patients with SHPT [36]. In Japanese haemodialysis patients with SHPT (iPTH  $\geq$  300 pg/mL), cinacalcet also decreased the serum PTH levels with favourable management of the serum P and Ca levels [37]. In addition, an analysis of the combined results from four similarly designed randomized, double-blinded, placebo-controlled clinical trials showed that cinacalcet treatment significantly decreased the risks of PTx, fracture and cardiovascular hospitalization [38]. In particular, the relative risk of PTx was much lower (93% reduction) with the cinacalcet treatment (RR 0.07) than with a placebo. These results suggest that cinacalcet makes it possible to manage SHPT in most patients without PTx. However, a considerable number of patients could not meet the targets of clinical guidelines for mineral bone parameters [36], especially those with nodular hyperplasia [39]. In addition, medical economic issues will be raised if the treatment with

cinacalcet becomes prolonged. It has been reported that cinacalcet might be more cost-effective in patients who have high risk of mortality or who expect to receive a kidney transplant soon. On the other hand, PTx might be more cost-effective in patients who have a considerable life expectancy [40,41]. A new alternative indication for PEIT may be examined in patients refractory to active vitamin D therapy. If PEIT destroys enlarged parathyroid glands completely or incompletely, it will be possible to reduce not only the dosage of cinacalcet, but also the drug expenditure. Because enlarged parathyroid glands, possibly nodular hyperplasia, express less CaSR, these glands are hyporesponsive to cinacalcet. Following selective PEIT for enlarged parathyroid glands, which are responsible for resistance to medical treatment, cinacalcet may be a more potent treatment for SHPT than active VD analogues. The clinical application of PEIT for severe SHPT may be expanded in combination with cinacalcet. Parathyroid intervention is still a useful tool for managing SHPT in the cinacalcet era.

## Conclusion

Parathyroid intervention is indispensable in order to achieve optimal management of SHPT. In Japan, PEIT has become widely used in the management of refractory SHPT as a less invasive alternative to PTx, particularly in patients with a single enlarged parathyroid gland. However, it still remains to be determined whether PEIT, as well as PTx, can improve hard outcomes, including hospitalization and mortality, over long periods. Further studies are necessary to confirm if parathyroid intervention facilitates better CKD-MBD management and leads to the improvement of clinical outcomes in long-term dialysis patients.

*Conflict of interest statement.* None declared.

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