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Pathophysiology of parathyroid hyperplasia in chronic kidney disease: preclinical and clinical basis for parathyroid intervention

Shunsuke Goto, Hirotaka Komaba and Masafumi Fukagawa

Division of Nephrology and Kidney Center, Kobe University School of Medicine, Kobe 650-0017, Japan

Abstract

Secondary hyperparathyroidism is characterised by excessive secretion of parathyroid hormone and parathyroid hyperplasia, resulting in both skeletal and extraskeletal consequences. Recent basic and clinical studies have brought considerable advances in our understanding of the pathophysiology of parathyroid hyperplasia and have also provided practical therapeutic approaches, especially with regard to indications for parathyroid intervention. In this context, it is quite important to recognize the development of nodular hyperplasia, because the cells in nodular hyperplasia are usually resistant to calcitriol treatment. Patients with nodular hyperplasia should undergo parathyroid intervention including percutaneous ethanol injection therapy (PEIT). Selective PEIT of the parathyroid gland is an effective approach in which the enlarged parathyroid gland with nodular hyperplasia is 'selectively' destroyed by ethanol injection, and other glands with diffuse hyperplasia are then managed by medical therapy. With a more focused attention to applying parathyroid intervention, we can expect significant improvement in the management of secondary hyperparathyroidism in dialysis patients.

Keywords: chronic kidney disease; fibroblast growth factor 23; parathyroid hyperplasia; parathyroid intervention; secondary hyperparathyroidism

Introduction

Secondary hyperparathyroidism develops universally in patients with chronic kidney disease (CKD), especially those on long-term dialysis therapy [1,2]. It is characterised by excessive secretion of parathyroid hormone (PTH) and parathyroid hyperplasia, resulting in bone disorder, soft tissue calcification and significantly increased risk of morbidity and mortality [3,4]. Despite recent progress in therapeutic modalities, severe hyperparathyroidism with marked hyperplasia usually becomes refractory to medical treatment [5]. Recent insights into the pathophysiological mechanisms underlying the development of parathyroid hyperplasia provide a rationale for selecting therapeutic strategies, including parathyroid intervention [5–7]. This article surveys the pathophysiological aspects of parathyroid hyperplasia in CKD and describes the potential of parathyroid intervention to attenuate this disorder, based on emerging data from preclinical and clinical studies.

Correspondence and offprint requests to: Masafumi Fukagawa, Division of Nephrology and Kidney Center, Kobe University School of Medicine, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan. Tel: +81-78-382-6500; Fax: +81-78-382-6509; E-mail: fukagawa@med.kobe-u.ac.jp

Secondary hyperparathyroidism in CKD

Ever since the observations of Albright *et al.* in 1937 [8], it has been known that chronic renal insufficiency is frequently accompanied by enlargement of the parathyroid glands and osteitis fibrosa cystica. Following the development of the first-generation PTH assay [9], elevated levels of PTH in patients with mild to moderate CKD were reported by Reiss *et al.* in 1969 [10]. Subsequent experimental studies have shown that a restriction of dietary phosphorus in proportion to the decrease in renal function can prevent the development of secondary hyperparathyroidism [11]. Consequently, Bricker proposed the 'trade-off hypothesis', which stated that phosphate retention, as a result of decreased renal function, would cause transient reduction of ionized calcium, which would in turn stimulate PTH secretion [12]. In other words, phosphorus retention and subsequent hypocalcaemia were considered to be major factors in the development of hyperparathyroidism. Several clinical studies produced substantial support for this proposal [13,14]; however, it has been shown that hypocalcaemia and hyperphosphataemia are not always present in patients with CKD, in whom serum PTH levels are already elevated [15,16]. Furthermore, experimental studies in which hypocalcaemia was prevented by feeding a high-calcium diet demonstrated a slight increase in PTH levels [17]. Thus, hypocalcaemia was not considered to be an essential factor for the development of hyperparathyroidism in CKD.

Decreased production of calcitriol also contributes to the development of secondary hyperparathyroidism [17]. Calcitriol has been shown to decrease PTH gene expression both *in vivo* and *in vitro* studies [18,19]. In the setting of CKD, decreases in nephron number lead to a decrease in the ability of the kidneys to produce calcitriol, thereby resulting in hyperparathyroidism. Several clinical studies demonstrated the mechanism and efficacy of calcitriol treatment

[20,21], and calcitriol and its analogues are the mainstays for the prevention and treatment of secondary hyperparathyroidism in dialysis patients [22,23]. The production of calcitriol is also regulated by phosphorus retention [15,24], because this can inhibit 1-α-hydroxylase. Thus, restriction of phosphate load might play a role, at least in part, in mediating the effects of calcitriol on hyperparathyroidism.

Phosphorus has also been considered to mediate parathyroid function directly, because several studies showed that dietary phosphorus restriction suppressed PTH hypersecretion independent of calcium or calcitriol [25,26]. This possibility was confirmed by *in vitro* studies that demonstrated that changes in extracellular phosphorus concentrations resulted in an increased secretion of PTH in the absence of changes in ionized calcium [27,28]. However, the manner in which phosphorus affects parathyroid function has not been fully elucidated. It has been shown that a type III phosphate transporter exists in parathyroid glands [29], but it is not known whether this transporter mediates the effects of phosphorus on PTH secretion. Recent detailed studies have suggested that phosphorus regulates the stability of PTH mRNA, and this effect seems to be mediated by Au-rich RNA-binding factor 1, proteins that bind to the PTH mRNA 3′ untranslated region [30,31]. It has also been demonstrated that phosphorus affects the production of arachidonic acid, a potent inhibitor of PTH release, thereby contributing to PTH hypersecretion [32].

Recent studies have helped to clarify the potential relationship between phosphorus retention and calcitriol deficiency by uncovering the role of fibroblast growth factor 23 (FGF23). FGF23 is a newly discovered peptide hormone involved in the pathogenesis of several hypophosphataemic diseases, such as X-linked hypophosphataemia [33], autosomal-dominant hypophosphataemic rickets [34] and tumour-induced osteomalacia [35]. Factors stimulating FGF23 secretion are dietary phosphate load [36] and the administration of calcitriol [37–39]. It has been shown that FGF23 is expressed primarily in osteocytes [40] and osteoblasts [41]. In the normal kidney, FGF23 acts to excrete phosphorus in the urine by decreasing mRNA and protein levels of the type IIa sodium phosphate cotransporter. FGF23 also suppresses calcitriol production by decreasing mRNA for 25-hydroxyvitamin D-1-α-hydroxylase [42]. In patients with CKD, serum FGF23 levels progressively increase as kidney function declines, even before the development of hyperphosphataemia [43–45]. Given that FGF23 physiologically promotes phosphaturia and suppresses the synthesis of calcitriol in response to phosphorus retention [36,42], it has been proposed that increasing levels of FGF23 in the setting of CKD prevent hyperphosphataemia, at the expense of low calcitriol and secondary hyperparathyroidism [46].

Development of parathyroid hyperplasia in CKD

Parathyroid cells are generally quiescent and rarely divide under normal physiological conditions [47], but the rate of cell proliferation can increase in response to mitogenic stimuli such as hypocalcaemia, calcitriol deficiency and phosphorus retention, as seen in the setting of CKD [1,48]. Thus, as kidney disease progresses, persistent hyperparathyroidism leads to the development of parathyroid hyperplasia. A similar phenomenon may also occur in many other endocrine organs, in which overactive secretion is generally associated with hypertrophy and/or hyperplasia; however, parathyroid hyperplasia in CKD is unique, in that the size and the nature of the glands may vary markedly in the same patient [2,7]. It is well accepted that development of parathyroid hyperplasia is associated with down-regulation of the vitamin D receptor (VDR) [49,50] and the calcium-sensing receptor (CaSR) [51,52]. As kidney disease progresses, parathyroid VDR and CaSR levels decrease in parallel with the severity of parathyroid hyperplasia. Besides the down-regulation of VDR and CaSR, changes in expression of various molecules have been observed in parathyroid hyperplasia [1]. Recently, enhanced parathyroid expression of the potent growth promoter transforming growth factor alpha (TGF-α) and its receptor, the epidermal growth factor receptor (EGFR), has been identified as one of the main causes of parathyroid hyperplasia and the reduction of VDR in CKD [53–55].

In the initial stage of CKD, the parathyroid glands secrete and synthesize PTH in response to increased demand, and parathyroid cells subsequently begin to proliferate, leading to diffuse hyperplasia [1]. Some cells in the parathyroid with diffuse hyperplasia escape from cell cycle control mechanisms and proliferate vigorously, forming small nodules, each of which is monoclonal in origin [7,56]. Such nodules are composed of more tightly packed cells featuring larger nuclei and a greater prevalence of cell cycle markers, oxyphil cells and acinar cell arrangements compared with those seen in diffuse hyperplasia [1]. When these nodules grossly enlarge and become encapsulated, the glands are termed as nodular hyperplasia. In the most severe cases, one of these nodules occupies the entire gland (single nodule) [2,7].

FGF23 and advanced hyperparathyroidism

As mentioned above, FGF23 is a new player in the classic ‘trade-off’ theory that has been proposed to explain the pathogenesis of secondary hyperparathyroidism [46]. Along with the decline of kidney function in CKD patients, serum intact FGF23 levels increase progressively [43–45]. Once patients are placed on dialysis therapy, serum FGF23 levels increase markedly, showing a positive correlation with serum phosphate levels and intact PTH levels. We have recently shown that measurement of the initial serum FGF23 level is a good screening test for predicting patients in whom secondary hyperparathyroidism will develop within 2 years [57]. We also demonstrated that serum FGF23 levels could be used as an additional marker for the resistance to intravenous calcitriol therapy in patients with established secondary hyperparathyroidism [58]. In another clinical study, we showed that intravenous calcitriol therapy not only suppressed PTH levels but also further increased serum FGF23 levels [37]. In accordance with this observation, it has recently been reported that calcitriol administration increased FGF23 levels *in vivo* and *in vitro* [38,39]. After surgical parathyroidectomy, serum FGF23 levels

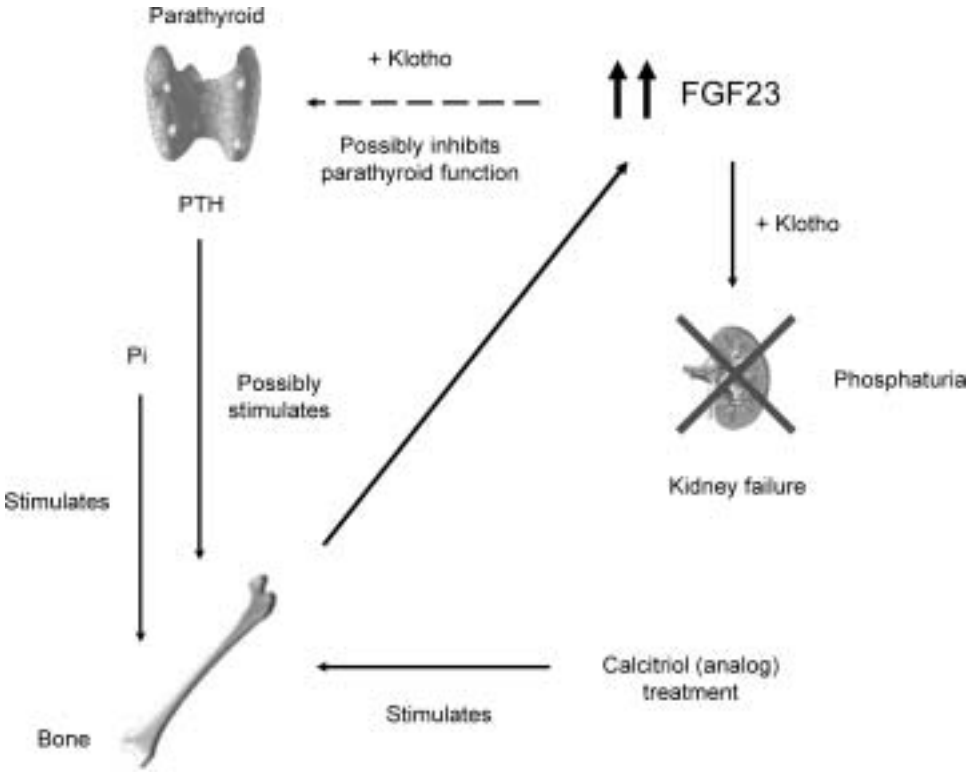

Fig. 1. The regulation and action of FGF23 without the functioning kidney. FGF23 production in the bone is continuously stimulated by phosphate load, calcitriol (analogue) treatment and possibly by high PTH. It remains to be elucidated whether very high FGF23 in dialysis patients would inhibit PTH expression by activating its cognate FGFRs in a Klotho-dependent fashion.

decrease gradually, indicating a possible association between abnormal PTH secretion and FGF23 regulation [59]. With regard to the skeletal effect of FGF23, a recent clinical study revealed that serum FGF23 level is not associated with decreased bone mineral density, nor with several circulating biomarkers of bone remodelling [60], despite the presence of the FGF receptor (FGFR) 1 in osteoblast and osteoclast cells [61].

Accordingly, it has been recognized that FGF23 production in dialysis patients is continuously stimulated by phosphate load, calcitriol (analogue) treatment and possibly by high PTH [2,46]; however, it remains unclear whether FGF23 directly modulates PTH expression, or whether the correlation is secondary to abnormalities in phosphorus and calcitriol metabolism. In this regard, the FGF23-klotho axis in regulating mineral homeostasis is a very attractive issue. It has been reported that FGF23 acts on its target tissues by binding to and activating its cognate FGFRs in the presence of its obligatory coreceptor, klotho [62,63]. Klotho binds to FGF23 and converts the canonical FGFR 1c to a receptor specific for FGF23 [63]. Administration of FGF23 to rats increases early growth response 1 (Egr-1) mRNA levels in the kidney and also in the parathyroid and pituitary [63]. Moreover, using both rats and *in vitro* rat parathyroid cultures, it has recently been shown that FGF23 directly suppresses both PTH secretion and its gene expression [64]. These findings may imply that FGF23, at least in part, has an inhibitory role in secondary hyperparathyroidism. Furthermore, it is also possible that the beneficial effects of calcitriol (analogue) treatment in secondary hyperparathyroidism may partly be attributed to an increase in FGF23. The resistance of the parathyroid to elevated levels of FGF23 in uraemia remains to be studied. Current understanding of the role of very high levels of serum FGF23 in severe hyperparathyroidism is summarized in Figure 1.

Refractory hyperparathyroidism with marked parathyroid hyperplasia

Development of hyperplasia not only leads to the increased volume of parathyroid mass but also to altered qualities, such as the down-regulation of VDR and CaSR. Nodular hyperplasia in patients with CKD is associated with a lower density of both CaSR and VDR than that noted in diffuse hyperplasia [49,50,52]. Density of VDR was reported to be negatively correlated with both the weight and proliferative activity of the glands [50]. These altered qualities are currently considered to be the central feature responsible for refractory hyperparathyroidism in patients with nodular hyperplasia [1,2]. Although calcitriol therapy may induce regression in glands with diffuse hyperplasia [65], regression of nodular hyperplasia may not occur except in those rare cases associated with spontaneous remission due to autoinfarction of the gland [66,67].

Several clinical and histological observations have shown that the size of the parathyroid gland, evaluated by

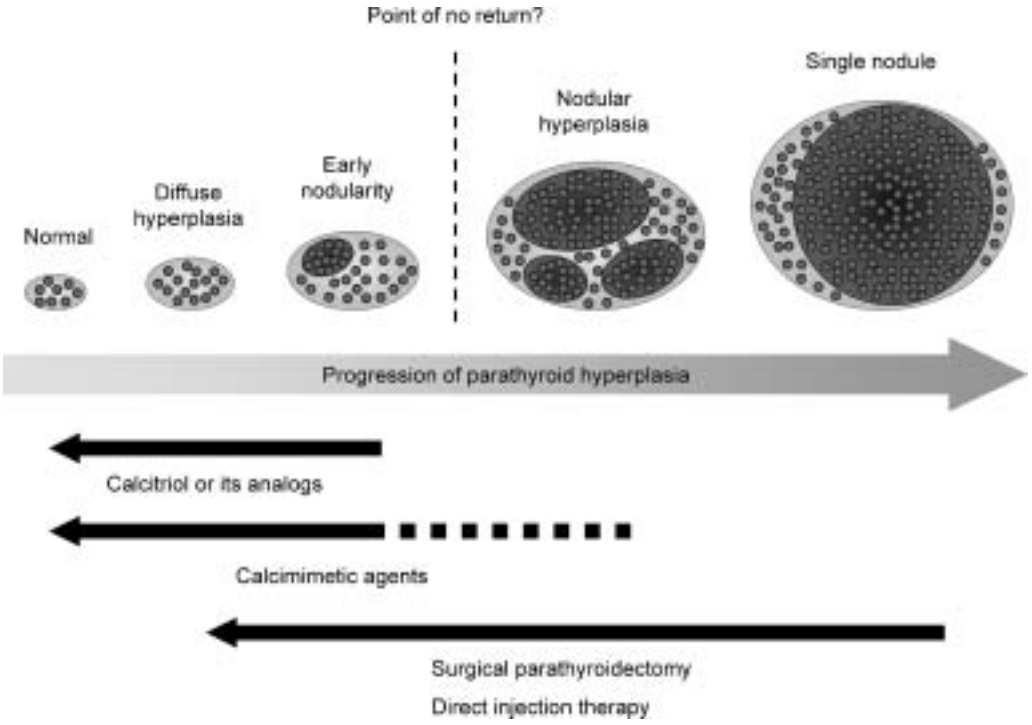

Fig. 2. Progression of parathyroid hyperplasia and current therapeutic strategy. Parathyroid intervention, such as surgical parathyroidectomy and direct injection therapy, is recommended for nodular hyperplasia refractory to calcitriol (analogue) treatment. Calcimimetic agents are promising tools, but further research is required to examine whether they can effectively control hyperparathyroidism associated with nodular hyperplasia.

ultrasonography, can be an indicator for the controllability of hyperparathyroidism. According to our clinical experience, patients with one or more enlarged glands larger than 0.5 cm^3 or 1 cm in diameter are usually refractory to calcitriol therapy in the long term [68]. Other researchers also reported that patients with enlarged parathyroid glands larger than 11 mm in diameter [69] or 300 mm^3 [70] were less responsive to maxacalcitol therapy than those with smaller glands. Histological studies reported that glands heavier than 0.5 g were composed of nodular hyperplasia in most cases [7]. Taken together, these findings suggest that the critical size is ∼0.5 cm^3 or 1 cm in diameter [5]. Patients with hyperplastic glands that meet this criterion should undergo parathyroid intervention, i.e. surgical parathyroidectomy and direct injection therapy, particularly if they do not respond to a short course of calcitriol (analogue) therapy [5] (Figure 2).

The selection of parathyroid intervention depends on the pattern of parathyroid hyperplasia. In patients with three or more enlarged parathyroid glands, there is consensus that surgical parathyroidectomy is indicated. Total parathyroidectomy with forearm autograft is preferred for secondary hyperparathyroidism, especially in patients who require long-term haemodialysis, because a recurrent, enlarged autograft can easily be removed from the forearm [71]. In contrast, direct injection therapy such as percutaneous ethanol injection therapy (PEIT) should be indicated for patients with only one or two enlarged glands. In a recent clinical study, PEIT was effective in patients with no more than one hyperplastic gland larger than 0.5 cm^3 [72]. The basis of PEIT is that enlarged parathyroid glands with nodular hyperplasia are destroyed 'selectively' by ethanol injection, and other glands with diffuse hyperplasia are then managed by adjuvant calcitriol (analogues) therapy. Another recent technique is direct calcitriol (analogue) injection therapy, which has been shown to induce the regression of nodular hyperplasia [73–75]. This therapy suppresses PTH levels and also restores the responsiveness of parathyroid cells to medical therapy. Recent studies have clearly shown that direct calcitriol injection not only induces apoptosis in parathyroid cells, but also up-regulates VDR and CaSR, resulting in normalization of the shifted sigmoidal curve between calcium and PTH [76].

Calcimimetic agents suppress parathyroid function by enhancing the sensitivity of the parathyroid CaSR to extracellular calcium ion levels [77]. Activation of the CaSR by calcimimetics allows long-term control of PTH in dialysis patients without increasing plasma levels of calcium, phosphorus and/or calcitriol [78,79]. We have also confirmed the efficacy of calcimimetics in reducing serum PTH levels in long-term dialysis patients [80]. However, it has not been fully elucidated whether patients with established nodular hyperplasia can be controlled by calcimimetics. With respect to this issue, recent clinical studies with calcimimetics in patients with hypercalcaemia due to persistent hyperparathyroidism after kidney transplantation seem to be promising [81–93]. Given that calcimimetics effectively suppressed PTH levels in such recipients with hypercalcaemia, in whom the numbers of VDRs and CaSRs remained reduced [84], calcimimetics might control severe hyperparathyroidism associated with nodular hyperplasia. Further clinical studies should be performed in the near

future to examine whether calcimimetics alone or in combination with calcitriol (analogue) can control hyperparathyroidism in CKD patients with nodular hyperplasia.

Conclusions

Detailed research in the past three decades has brought considerable advances in the understanding of basic and clinical aspects of parathyroid hyperplasia. Recent data from preclinical and clinical studies have provided practical therapeutic approaches, especially with regard to the indications for parathyroid intervention. With a more focused attention to applying parathyroid intervention to patients with nodular hyperplasia, we can expect a significant improvement in morbidity and mortality among CKD patients. Further research and progress in this area are required to establish a more rational approach with a view towards improving patient outcomes.

Conflict of interest statement. None declared.

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