Can Hyperparathyroid Bone Disease Be Arrested or Reversed?

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Parathyroid hyperplasia, oversecretion of parathyroid hormone (PTH), and hyperparathyroid bone disease are characteristic features of chronic uremia; they develop early in the course of uremia and often in a progressive way. This review focuses on the potential for arrest or regression of hyperparathyroid-induced bone disease. For this purpose, the review addresses investigations that have used bone histology and not investigations that indirectly attempted to demonstrate changes in the skeleton by measurements of bone mineral density or laboratory indices of bone turnover, other than PTH. A prerequisite for inducing regression of the hyperparathyroid bone disease is a significant suppression of PTH secretion or reversal of hyperparathyroidism and uremia. It is concluded, on the basis of paired bone biopsy studies in patients with established hyperparathyroid bone disease, that bone histology can be improved or normalized after treatment that diminishes PTH levels. Oversuppression of PTH levels, however, might lead to adynamic bone disease.


Renal osteodystrophy (ROD) is a disabling skeletal disease in uremic patients that consists of a high-turnover bone disease, a low-turnover bone disease, or a mixture of both. The type of bone lesion is correlated to increased production or to oversuppression of parathyroid hormone (PTH) levels (1–3).

The high-turnover bone disease, osteitis fibrosa (cystica), is related to the severity of the secondary hyperparathyroidism (sHPT). PTH in concert with locally produced cytokines and factors (some produced by bone marrow cells and some by osteoblast precursors) IL-1 and TNF and later IL-6, IL-11, GM-CSF, M-CSF, and the OPG/RANKL system induce recruitment and differentiation of osteoclast precursors, resulting in stimulation of bone resorption (4). Bone formation is impaired, but the mechanism is not completely understood. PTH inhibits the synthesis of collagen and inhibits the progression of the osteoblastic cell cycle. The net result of severe sHPT in uremia is accelerated bone resorption. Furthermore, these bone lesions are characterized by massive peritrabecular fibrosis, and it has been postulated that PTH stimulates proliferation of an osteoprogenitor (preosteoblastic cell), which leads to accumulation of fibroblastic cells that produce narrow fibrosis (4). Recent experimental evidence (5,6) documented that uremia, per se, decreases skeletal anabolic activity. Development of HPT might be considered an adaptive mechanism to override this abnormality in bone remodeling. In this respect, increased PTH functions as a surrogate for a missing factor, maintaining bone turnover. Bone morphogenetic protein 7 is a candidate for such a renal-derived factor (7,8).

The clinical consequences of osteitis fibrosa, fractures, skeletal deformities, tendon rupture, bone pain, and impaired skeletal growth in children are well described. In the total population of uremic patients, hyperparathyroid bone lesions still are the most frequent and associated with the most severe morbidity. Thus, osteitis fibrosa targets the most important role of the skeleton, as a site where muscles and tendons are attached and as a rigid framework that facilitates bodily movements.

Focus recently has been on the association between ROD and calcium homeostasis in general. There is a difference between the bone remodeling system and the calcium homeostatic system. It widely has been believed that plasma ionized calcium (Ca$^{2+}$) concentration is regulated by the rate of bone resorption, a concept that probably is wrong. Plasma Ca$^{2+}$ levels depend on an equilibrium between systemic and bone extracellular fluid (ECF) at quiescent bone surfaces (9). This equilibrium is set by calcitropic hormones, including PTH and 1,25-(OH)$_2$D (calcitriol) (10,11). In the absence of kidney insufficiency, high plasma PTH will set the equilibrium between bone and ECF at a higher level, resulting in hypercalcemia, and deviations of plasma Ca$^{2+}$ from this level will be corrected rapidly by a flux of calcium over the bone/ECF barrier (12). How the hyperparathyroid stage in chronic uremia affects calcium homeostasis is less clear. In hyperparathyroid ROD, a paradox exists, as increased bone resorption and increased PTH levels are associated not with hypercalcemia but with hypocalcemia (12), indicating an abnormal setting of the equilibrium. The consequences of disturbed calcium and phosphate metabolism in sHPT go beyond skeletal problems. Hyperphosphatemia is a powerful predictor of cardial death, mediated via vascular calcifications (13). Advanced HPT also is accompanied by disturbances in lipid metabolism,
anemia and resistance to erythropoietin, and dysfunction of the immune and endocrine systems (14,15).

The present review focuses on the arrest or reversal of hyperparathyroid-induced bone disease. For this purpose, we address only investigations in which a documented effect on already-established hyperparathyroid bone disease has been demonstrated. We do not address prevention of hyperparathyroid bone disease or the many investigations that have attempted indirectly to demonstrate changes in the skeleton by measurements of bone mineral density or markers of bone turnover, other than PTH. The present understanding of the impact of parathyroid hyperplasia on PTH secretion is reviewed briefly, because a prerequisite for inducing regression of the hyperparathyroid bone disease is arrest or reversal of HPT or at least a significant suppression of PTH secretion.

Can Parathyroid Hyperplasia Be Arrested or Reversed?

In advanced uremia, PTH levels should be controlled at a moderately elevated level to promote normal bone turnover, as indicated by the Kidney Disease Outcomes Quality Initiative Guidelines on Bone and Mineral Metabolism (16). As such, a certain degree of parathyroid hyperplasia has to be accepted. Uremia is associated with parathyroid growth. Experimental studies have demonstrated that proliferation of the parathyroid cells (PC) is induced by uremia and further promoted by hypocalcemia, phosphorus retention, and vitamin D deficiency (17). Conversely, PC proliferation might be arrested by treatment with a low-phosphate diet, vitamin D analogs, or calcimimetics. An important question is whether regression of parathyroid hyperplasia can be induced. Can the increased glandular mass that is seen in uremia be normalized? Such a reduction of parathyroid mass would call for massive apoptosis to take place. This question has not yet been resolved. The parathyroids have an extremely low cell turnover and probably a poorly developed program for cell deletion. The number of apoptotic cells in normal human parathyroids is very low, 1/10,000 PC as reported by Zhang et al. (18). In rat models, several studies have been unable to find evidence for programmed PC death in normal or hyperplastic parathyroid tissue (19–21). There are no known stimuli for apoptosis in the PC (22), although an effect of vitamin D has not been excluded completely (23–26). The evidence for induction of massive apoptosis by calcitriol still is contradictory, however. In a clinical study of Quarles et al. (27), long-term intensive calcitriol therapy failed to decrease the volume of parathyroid glandular mass, as assessed by high-resolution ultrasound and/or magnetic resonance imaging. In contrast, Fukagawa et al. (24) found in patients who were on long-term dialysis that oral calcitriol pulse therapy induced a 40% reduction of the parathyroid volume, as measured by ultrasound after 12 wk of treatment, with most of the volume reduction occurring during the first 4 wk. The ultrasound method was reproducible, but its accuracy is unknown. In 1977, Henry et al. (23) examined parathyroid glands of 3-mo-old vitamin D–deficient chickens that received vitamin D replacement. In that study, a clear reduction in the number of PC was seen on the basis of reductions in glandular weight, protein, and DNA content (23). The changes were detectable within 4 d and could have resulted only from apoptosis. Recently, a significant induction of apoptosis was demonstrated by 22-oxa-1,25-dihydroxyvitamin D$_3$ maxacalcitol injection directly into the parathyroid glands of uremic rats by Shizizaki et al. (26). The process of apoptosis was assessed directly by the transferase-mediated dUTP nick-end labeling method for identification of DNA fragmentation. The quantity of apoptotic cells was increased further by repetitive intraglandular injections of maxacalcitol. Not all studies have found similar results, however. In a study on rats by Szabo et al. (28), 10 d of treatment with calcitriol from day 21 of uremia did not reverse existing hyperplasia. Furthermore, no apoptosis of the parathyroids could be induced in uremic rats, even by extremely high doses of calcitriol as reported by Naveh-Many et al. (20) and Jara et al. (29). In vitro, however, calcitriol even has been shown to inhibit both PC proliferation and apoptosis (30). Recently, Colloton et al. (31) showed in uremic rats that administration of the calcium receptor (CaR) agonist cinacalcet HCl for 4 wk significantly reduced parathyroid weight. However, the authors were unable to provide a mechanism for the observed decrease in parathyroid tissue mass and failed to detect evidence for enhanced parathyroid apoptosis.

Several clinical studies have documented that PTH levels can be suppressed in most uremic patients and that this suppression can be maintained by continuous treatment with phosphate binders, vitamin D analogs, or calcimimetics (32–42). PTH levels return to pretreatment values, however, when the treatment is stopped (32,33,37). This rebound of PTH levels suggests that even with good control of parathyroid function under maintenance treatment, no involution of hyperplastic glands takes place. As such, in the clinical situation, no convincing evidence that apoptosis takes place in hyperplastic parathyroid tissue or that there is involution of parathyroid hyperplasia by current treatment regimens exists. The induction of apoptosis is of potential relevance for the control of parathyroid hyperplasia. Effective and selective manipulation of the mechanisms that lead to programmed cell death might have therapeutic consequences. The use of the cell’s own mechanisms for elimination might be rational, because the adverse effects can be minimized and because the process can be operated in a specific direction. The requirement is that the function of apoptosis be intact and can be induced. In this context, it is an important observation by Shizizaki et al. (26) that PC in hyperplasia are able to undergo apoptosis. The condition for a potential reversal of hyperparathyroid bone disease must be regression of increased parathyroid mass and/or a sufficient suppression of PTH secretion.

Regression of Parathyroid Hyperplasia Is Not Necessary for Normalization of PTH Levels

When the uremic condition is lifted or reversed (by remission of the kidney disease or by a successful kidney transplantation), plasma PTH levels can be normalized, even though a considerable degree of hyperplasia still is present (43,44). As such,
only a minority of patients who receive a transplant require parathyroidectomy (PTX) (45–48). Experimentally, it has been shown clearly that even considerable parathyroid hyperplasia can be controlled when the functional demand for increased PTH levels is abolished and a normal kidney function is present. When 20 isogenic parathyroid glands were implanted into one parathyroidectomized rat, a short-lasting hypercalcemia was induced, soon followed, however, by normalization of Ca\(^{2+}\) and PTH levels. Normal suppressibility of PTH secretion by high Ca\(^{2+}\) was obtained in normal rats with 20 parathyroid glands implanted. Similarly, normal levels of Ca\(^{2+}\) and PTH and normal suppressibility of PTH secretion were attained when eight isogenic glands from uremic rats were implanted into normal rats or when long-term uremia and severe sHPT was reversed by an isogenic kidney transplantation (43,44). Normalization of PTH levels after experimental kidney transplantation took place despite a persistent decrease of vitamin D receptor mRNA and CaR mRNA in the parathyroids (43). When eight isogenic glands from normal rats were implanted into each previously hyperparathyroid, now parathyroidectomized, uremic rat, a similar degree of HPT developed, as when the rats had their own two parathyroid glands present (44). Therefore, in experimental models, PTH levels are determined by the functional demand and not by parathyroid mass, per se.

In the clinical situation, however, a subgroup of patients with severe sHPT are refractory to treatment or develop tertiary HPT after a successful kidney transplantation. When nonsuppressible sHPT or tertiary HPT is present in patients who are referred for PTX, nodular hyperplasia with differences in gene expression between different nodules has been observed in most cases. Furthermore, an altered expression of some autocrine/paracrine factors has been demonstrated in the nodules (49), e.g., enhanced expression of PTH-related peptide (50), a potent stimulator of PTH secretion (51,52). Therefore, the altered quality of the parathyroid mass and not only the increased parathyroid mass, per se, might be responsible for noncontrollable HPT in uremia and after kidney transplantation.

**Reversal of Hyperparathyroid Bone Disease**

**Vitamin D Analogs**

Only a few studies have examined the reversal of established ROD, especially of hyperparathyroid bone disease, by treatment with vitamin D analogs, and these include only small numbers of patients, in contrast to the large number of clinical and experimental studies that have demonstrated and confirmed the effect of vitamin D analogs on suppression of PTH synthesis and secretion (53,54), an effect that may be suggestive also for an effect on PTH-induced bone disease.

Histomorphometric studies that were based on bone biopsies have documented a beneficial effect of treatment with vitamin D analogs in uremic patients with sHPT. Improvement of osteitis fibrosa in hemodialysis patients after treatment with 1,25(OH)\(_2\)D\(_3\) or 1α(OH)D\(_3\) was described already in 1977 by Coburn *et al.* (55). Thirty-nine patients were evaluated with bone histology and a disability score. Reversal of symptoms of severe osteitis fibrosa was impressive. In some instances, the patients were able to walk after being totally bedridden. Improvement of myopathy was prominent and correlated to a fall in alkaline phosphatase. Thirteen patients did not respond to treatment; in seven cases, skeletal biopsy revealed the appearance of an inactive skeleton and abundant unmineralized osteoid (described before the knowledge of aluminum toxicity, the patients were treated with Al-containing P-binders). The remainder of the nonresponders had marked parathyroid hyperplasia. Similar findings were reported the same year by Melsen *et al.* (56), who examined 12 uremic patients with bone biopsies before and after 6 mo of treatment with 1α(OH)D\(_3\).

*Andress et al.* (57) evaluated in 1989 the effectiveness of long-term (11.5 mo) intermittent 1,25(OH)\(_2\)D\(_3\) infusions as treatment for severe osteitis fibrosa in 12 patients who were on hemodialysis and whose bone disease was refractory to oral therapy. The treatment was effective in ameliorating osteitis fibrosa, although the majority of patients had hypercalcemic episodes. In a large placebo-controlled study, Hamdy *et al.* (38) examined 176 patients who had mild to moderate renal failure and underwent bone biopsies at the start and at the end of a 2-yr treatment period with 1α(OH)D\(_3\) (average 0.25 μg/d). Among a total of 132 patients with abnormal bone histology before treatment, bone disease resolved in 42% of those who were given 1α(OH)D\(_3\) with a decrease in marrow fibrosis and a decrease in bone turnover, as compared with 4% in the placebo-treated control group.

*Nordal et al.* (58) concluded in a study on 13 predialysis patients who underwent biopsy before start of treatment with 1,25(OH)\(_2\)D\(_3\) and at the time of transplantation that a beneficial effect was seen only in patients who started treatment with a GFR >30 ml/min. Fourteen children and adolescents with sHPT and biopsy-proven hyperparathyroid bone disease received intermittent oral or intraperitoneal doses of 1,25(OH)\(_2\)D\(_3\) for 12 mo in a study by Goodman *et al.* (59). Improvement of histologic indices of hyperparathyroid bone disease was seen in 12 of 14 patients, and osteitis fibrosa resolved in 10 of 11 patients. Bone formation normalized in six patients, whereas another six patients developed adynamic bone lesions. There was no control group in this study, however, and the results were not corrected for possible confounding factors, such as high calcium intake and/or calcium-based phosphate binders. In this respect, it should be stressed that an enhanced calcium load in animal studies seems to be of great importance for the development of an adynamic bone disease as shown in several studies by Sanchez *et al.* (60–62), and the general concept today is that massive oral calcium supplementation favors adynamic bone disease, whereas moderate amounts of oral calcium will be able to control sHPT without inducing low bone turnover.

The search therefore has been on “less calcemic vitamin D analogs.” The effect of such compounds on hyperparathyroid bone disease has been examined until now only in experimental animals. Two months of treatment with 19-Nor-1,25(OH)\(_2\)D\(_3\) improved bone histology in uremic rats with established hyperparathyroid bone disease (63). In nephrectomized dogs that were uremic for >1 yr and kept on a high-P diet, 1,25-(OH)\(_2\)22-oxa-D\(_3\) reversed abnormal bone formation such as woven osteoid and fibrosis, improved mineralization parameters, but did not significantly alter the level of bone turnover. It therefore
was concluded that the compound might be less likely to induce adynamic bone disease (64).

In conclusion, besides having a beneficial effect on the vitamin D–deficient bone disease osteomalacia, therapy with vitamin D analogs as treatment of sHPT might improve the accompanying hyperparathyroid bone disease. The limitations, however, are that very severe sHPT can be refractory to treatment with vitamin D analogs and that overtreatment might result in the development of adynamic bone disease.

Calcimimetics

No clinical studies and only one experimental study on calcimimetic treatment of established hyperparathyroid bone disease exist at the moment. In rats that were uremic for 6 mo Wada et al. (65) demonstrated that treatment with the calcimimetic compound NPS R-568 for 30 d ameliorated the already present osteitis fibrosa and at the same time increased cortical bone strength and bone stiffness. Potentially, CaR agonists may become an interesting treatment of hyperparathyroid bone disease in the future, because their daily administration is known to induce continuous fluctuations of plasma PTH levels. Because intermittent PTH treatment in osteoporosis has been shown to promote bone formation over bone resorption, it is possible that daily changes in circulation PTH act in a similar way (66).

PTH

Total or subtotal PTX is the radical choice for treatment of severe HPT and as such might also be of benefit for the presence of hyperparathyroid bone disease. The very early changes that occur after PTX were studied by Yajima et al. (67), who performed bone histomorphometry in 14 patients with severe sHPT before and 1 wk after PTX. Bone resorption was suppressed rapidly with complete disappearance of the osteoclasts, and a marked increase in bone formation was observed at that early stage, whereas disappearance of fibrous tissue was not yet observed.

A partial beneficial long-term effect was reported already in 1985 by Charhon et al. (68), who performed bone histomorphometry in 10 patients before and again 10 to 16 mo after subtotal PTX. Despite that most of the patients still had significantly elevated PTH levels after PTX, this procedure was effective in correcting the severe bone lesions that were related to HPT. The regression of the bone lesions was incomplete, however, in six of the 10 patients because resorption surfaces and osteoclast numbers remained elevated in these patients, still with considerably elevated PTH levels. The degree of fibrosis was markedly reduced all patients. Furthermore, the excessive reduction of PTH secretion led to inactive bone. Similar, low or normal bone turnover was reported by Kaye et al. (69) in five patients who were examined before and >1 yr after total PTX.

Santos et al. (70) also studied the long-term response of hyperparathyroid bone disease to PTX and followed nine patients who had chronic uremia and were on hemodialysis with bone biopsies before and 1 yr after total PTX with autoimplantation in the forearm. The patients had severe HPT that was unresponsive to vitamin D therapy; four patients had osteitis fibrosa, and five had mixed lesions before PTX. One year after PTX, circulating PTH levels were low, just above normal range, and regression of hyperparathyroid bone lesions was complete in eight patients, whereas one still had mild lesions. Bone marrow fibrosis regressed in all patients. However, osteomalacia or adynamic bone disease was found in six patients. Seventy-four percent of the patients were on low-dose 1,25(OH)2D3 therapy after PTX.

In conclusion, despite often severe histologic changes, hyperparathyroid bone disease might regress after correction of the stage of sHPT by PTX. Low levels of PTH, however, might result in the creation of an adynamic bone disease.

Kidney Transplantation

A successful kidney transplantation will normalize the abnormalities in mineral homeostasis. After kidney transplantation, plasma PTH falls in most patients with sHPT, despite previous long-term uremia (71). Part of this fall might be due to clearance of C-terminal PTH fragments as a result of the improvement in GFR, because most assays that have been used until recently co-measure some long C-terminal PTH fragments (72–74). In most cases, plasma PTH returns to near normal over time, although not all studies are confirmatory (75). The normalization of GFR, however, seems to be decisive for the normalization of the PTH levels (48,76–78). The renal 1α-hydroxylase activity is restored within weeks to months. Phosphorus retention is eliminated. New problems arise, however, as a result of the detrimental skeletal effects of the immunosuppressive therapy, especially glucocorticoids and calcineurin inhibitors. Only a few and small studies exist on bone histology after kidney transplantation. Important information was provided by Rojas et al. (79) on the very early changes in bone histology in 20 patients, on average 35 d after transplantation. Eleven of these patients also had bone biopsies performed on the day of transplantation. The data revealed impaired osteoblastogenesis and early osteoblast apoptosis, possibly induced by the high doses of glucocorticoids at this early stage. It is interesting that PTH seemed to have a protective effect by preserving osteoblast survival. The peritrabecular fibrosis was markedly decreased. In another study that used paired bone biopsies, Cruz et al. (80) studied 20 patients before and 6 mo after transplantation. Eight patients had varying degrees of hyperparathyroid bone disease before and a marked reduction of both osteoclastic surface and eroded surface after transplantation, together with disappearance of fibrosis. Similar findings were reported by Coco et al. (81) in four control patients with hyperparathyroid bone disease. In this study, another group of five patients with hyperparathyroid bone disease were given pamidronate. All five patients developed adynamic bone at 6 mo after transplantation.

Similar to the beneficial effect of PTX on the regression of hyperparathyroid bone disease, normalization of PTH secretion after a successful kidney transplantation results in improvement of the skeleton. The results after transplantation, however, often are severely disturbed by the need for simultaneous immunosuppressive treatment, which by itself has a negative effect on the skeleton.
Conclusion
The hyperparathyroid bone disease osteitis fibrosa is a high-turnover bone disease characterized by increased number and activity of osteoclasts, increased bone resorption, and increased activity of osteoblasts, resulting in overproduction of collagen and leading to periarticular and bone marrow fibrosis. In advanced uremia, PTH levels should be controlled at a moderately elevated level to promote normal bone turnover. Parathyroid hyperplasia is poorly reversible. However, even when considerably increased parathyroid mass is present, PTH secretion still can be controlled, depending on the functional demand. As such, development of a certain degree of parathyroid hyperplasia might be accepted. In patients with established hyperparathyroid bone disease, paired bone biopsies that are obtained before and after treatment that diminishes PTH levels indicate that bone histology can be improved or normalized with disappearance of fibrous tissue. It is not known, however, whether the beneficial changes in bone histology after reduction of PTH levels result in normal bone structure and normal bone strength. Treatment of hyperparathyroid bone disease requires a delicate balance, as overreduction of PTH levels leads to development of adynamic bone disease.

References


