

Renal osteodystrophy with special emphasis on secondary hyperparathyroidism

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ABSTRACT

Chronic uraemia is associated with severe disturbances in the calcium, phosphorus and vitamin D homeostasis, leading to the development of secondary hyperparathyroidism (HPT) with increased biosynthesis and secretion of parathyroid hormone (PTH) and hyperplasia of the parathyroid glands. Renal osteodystrophy (ROD) is a frequent and serious complication in chronic uraemic patients, which in a majority of patients is secondary to the severe disturbances in parathyroid homeostasis with high PTH levels leading to a high turnover bone disease, osteitis fibrosa, and with low PTH levels leading to a low turnover bone disease, the adynamic bone disease.

Therapeutic strategies with a beneficial pre-

ventive and/or therapeutic effect on HPT and the accompanying ROD in chronic uraemia include phosphate restriction, phosphate binders, low calcium dialysate, vitamin D analogs and calcimimetics.

SECONDARY HYPERPARATHYROIDISM IN URAEMIA

Secondary hyperparathyroidism (sec. HPT) develops early in renal insufficiency and may affect the function of several organs¹⁻³. The stimuli for the development of sec. HPT of relevance to renal failure are hypocalcaemia, hyperphosphatemia and low levels of 1,25(OH)₂D⁴⁻⁸. Hypocalcaemia increases the PTH gene expression per parathyroid cell, in-

creases the secretion of mature PTH from the parathyroid cells, and increases the number of parathyroid cells^{4,5,9}. The effect of low calcium on PTH gene expression is posttranscriptional^{10,11}. The extra cellular Ca^{2+} depending suppression of PTH secretion is mediated via the calcium-sensing receptor (CaR) that is located on the surface of the parathyroid cells¹². Expression of the CaR mRNA and protein is diminished in human parathyroid glands of advanced uraemia and in rat parathyroids of 5/6 nephrectomized rats, indicating an impaired sensitivity to extra cellular calcium in uraemia¹³⁻¹⁶. In addition to reducing the plasma Ca^{2+} concentration hyperphosphatemia has a calcium independent direct effect on the regulation of PTH secretion, as demonstrated in *in vitro* models in rat, bovine and human parathyroid glands^{8,17-19}. The mechanism is posttranscriptional¹¹. The cellular target for phosphate is still unknown⁵. $1,25(\text{OH})_2\text{D}_3$ (Calcitriol) is an important regulator of the PTH gene and may play a specific role in the control of the glandular mass²⁰⁻²². Pharmacological doses of calcitriol decrease PTH gene expression at the transcriptional level by binding the $1,25(\text{OH})_2\text{D}_3$ receptor (VDR) to a vitamin D-responsive element on the PTH gene promoter^{23,24}. The levels of calcitriol in mild and moderate uraemia are maintained within the normal range at the expense of elevated PTH levels. In uraemia low levels of VDR have been demonstrated in the parathyroid cells^{6,13,25}, together with an impaired affinity of vitamin D to its receptor, resulting in a reduced activity of calcitriol²⁶. Furthermore, uraemia per se enhances the stability of PTH mRNA by a posttranscriptional mechanism that decreases the degradation of RNA, independent of changes in circulating levels of calcium and phosphate²⁷. The factors that are responsible for the degradation of PTH in the parathyroid cell are probably cytosolic endonucleases^{11,28}. Such factors

are selectively decreased in uraemia²⁷. Other factors that are regulating the secretion of PTH include some of autocrine or paracrine nature^{13,29}. Such an autocrine/paracrine regulation might be involved in the induction of sec. HPT¹³. In addition to increased levels of intact PTH, produced by the parathyroid glands, an accumulation of C-terminal PTH fragments takes place in uraemia. A specific effect of some of these fragment has been proposed, possibly via a unique receptor³⁰, but the biological significance of such a receptor remains unknown. The expression of all these factors may be influenced by the chronic uraemia^{31,32}. As such, hyperparathyroidism associated with chronic uraemia results from a combination of functional and structural changes in the parathyroid glands, as shown in Figure 1.

HYPERPLASIA OF THE PARATHYROID GLANDS

Parathyroid tissue is a discontinuous replicator tissue, which is characterized by a low cell turnover, a low rate of mitosis, and no separate stem cells^{9,33}. As estimated by Parfitt the mean life span of normal parathyroid cell is 20 years in humans and 2 years in rats^{33,34}. Mitosis can be stimulated by functional demand. In human subjects parathyroid growth progresses in response to chronic renal failure through several stages from diffuse hyperplasia to nodular hyperplasia and to formation of adenomas. Diffuse hyperplasia is initiated by hypocalcaemia and phosphorus retention and becomes more severe as the result of calcitriol deficiency³⁵. The next stage is that hyperplasia becomes nodular and the glandular enlargement asymmetrical. The nodules consist of cells that are more closely packed with large nuclei, an increased prevalence of mitosis and depletion of VDR and

CaR^{16,36,37}. Detailed histochemical and immunochemical studies indicate similarity in gene expression between the cells in each nodule, but differences between nodules^{36,38}. Monoclonal growth of the parathyroid cells has been found in a majority of the uraemic patients with refractory hyperparathyroidism³⁹. The genes responsible for monoclonality have not been identified. Apparently, somatic mutations confer a growth advantage to clones of parathyroid cells, which causes monoclonal growth and nodular parathyroid hyperplasia, although these two phenomena are not strictly linked. The next stage is emergence of an adenoma in one or occasionally more than one of the nodules, as an expression of a mutation in one of the cells that are undergoing the most rapid proliferation. In some cases there is a loss of a tumor suppressor gene on chromosome 11, a molecular defect with the potential for disrupting the control of the cell cycle⁴⁰. The final and least common stage is malignant transformation leading to parathyroid carcinoma, an event reported in 5 patients on long term haemodialysis⁴¹. It seems that at the initial stages development of parathyroid hyperplasia is a regulatory phenomenon, but that during the progression it escapes from normal growth control.

The precise role of the disturbances in calcium, phosphorus and calcitriol levels for the development of abnormal parathyroid growth in uraemia, as well as the precise role of these factors in the regulation of normal parathyroid growth have not been well established. Calcium deficiency together with calcitriol deficiency are probably the most important stimuli for parathyroid hyperplasia, as it has been shown *in vivo* in uraemic rats by Naveh-Many *et al.*⁴. A concomitant decrease in the expressions of CaR and VDR as described in the parathyroid glands of uraemic rats^{13,42} and chronic dialysis patients^{13,16,43} should theoretically enhance par-

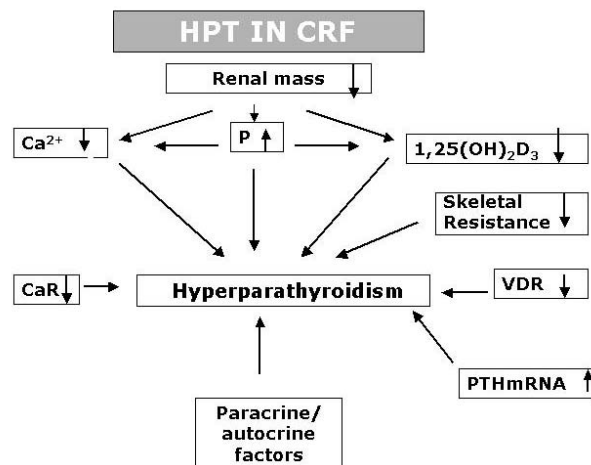


Figure 1. A schematic presentation of some of the many factors involved in the development of secondary hyperparathyroidism in chronic uraemia.

athyroid cell proliferation even further. This was proven indirectly by the observation that administration of a calcium-sensing receptor agonist, NPS-R568, or calcitriol led to the suppression of parathyroid cell proliferation in uraemic rats^{44,45}.

The role of phosphorus accumulation in parathyroid cell growth is documented in several studies in uraemic rats^{4,7,42}. Conversely, an early dietary phosphate restriction prevented parathyroid cell proliferation and over secretion of PTH in uraemic rats^{8,46,47}. Furthermore, it has been found in uraemic rats that hyperphosphatemia induced parathyroid cell hyperplasia, even when changes in plasma calcium and calcitriol were carefully avoided, pointing towards a direct effect of phosphorus on cell proliferation⁴.

Thus, in uraemia severe disturbances exist in the many parameters related to calcium homeostasis, resulting in severe disturbances in the important target organ - the skeleton.

RENAL OSTEODYSTROPHY

Renal osteodystrophy (ROD) is a disabling skeletal disease in uraemic patients consisting of either 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 over suppression of PTH levels⁴⁸⁻⁵⁰.

The high turnover bone disease, osteitis fibrosa (cystica) is related to the severity of the sec. HPT. PTH in concert with locally produced cytokines and factors (some produced by bone marrow cells and some by osteoblast precursors), IL-1, TNF and later IL-6, IL-11, GM-CSF, M-CSF induce recruitment and differentiation of osteoclast precursors resulting in stimulation of bone reabsorption⁵¹. 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 sec. HPT in uraemia is accelerated bone reabsorption. Furthermore, these bone lesions are characterized by massive peritrabecular fibrosis and recently it has been postulated that PTH stimulates proliferation of an osteoprogenitor which leads to accumulation of fibroblastic cells producing marrow fibrosis⁵¹. The clinical consequences of osteitis fibrosa, fractures, skeletal deformities, tendon rupture and bone pain are well described. In the total population of uraemic patients the hyperparathyroid bone lesions are still the most frequent and associated with the most severe morbidity. Thus, osteitis fibrosa cystica targets the most important role of the skeleton, as a site where muscles and tendons are attached and as a rigid framework which facilitates bodily movements.

A low turnover bone disease is seen in patients with osteomalacia due to the low $1,25(\text{OH})_2\text{D}_3$ levels, due to aluminium intoxica-

tion or might be seen as a special form of bone disease, the adynamic or aplastic bone disease⁵². Osteomalacia is characterized by an increased amount of unmineralized osteoid bone. Mineralization of bone matrix depends upon the presence of adequate supply of vitamin D in the form of its active metabolite, $1,25(\text{OH})_2\text{D}_3$, but also of calcium, and phosphorus and of the presence of a normal pH. The precise role of vitamin D in the mineralization process is not clear, just as the exact mechanism involved in the development of uraemic osteomalacia is not clear. In uraemia all factors necessary for the appropriate mineralization process might be disturbed. Today, adequate correction of acidosis and sufficient supplementation with calcium, vitamin D and protein has made overt osteomalacia a rare component of uraemic osteodystrophy.

Adynamic bone disease is diagnosed with increased frequency^{48,50,52-54}. It was previously the predominant type of uraemic osteodystrophy in aluminium intoxicated uraemic patients. Today, adynamic bone disease is especially seen in uraemic patients with rather low levels of PTH, such as in patients with diabetic nephropathy and in patients on Continuous Ambulatory Peritoneal Dialysis, CAPD. It is, therefore, postulated that the uraemic organism needs an increased level of PTH (two to three times upper normal level) in order to maintain normal bone remodelling⁵¹. The mechanism behind this increased need for PTH could be skeletal resistance to the action of PTH, a condition which is well documented in uraemia^{55,56}. Another possibility is lack of a bone remodelling regulation factor or factors which might be compensated for by the secondary HPT. It has recently been speculated that bone morphogenetic protein-7 could be such a systemic factor. This protein is produced by normal renal tubular cells and is a potent activator of the osteoblast diffe-

rentiation⁵¹. The clinical symptoms arising from the adynamic bone disease are far less well characterized than those of osteitis fibrosa and osteomalacia. Patients with adynamic bone disease have an increased risk of developing hypercalcemia when exposed to high calcium dialysate or vitamin D treatment. In this situation we probably focus upon another important function of the skeleton, as an organ participating in the calcium homeostasis. Uraemic patients with adynamic bone disease are not able to incorporate a calcium load into the bones to the same degree as subjects with a normal skeleton. Whether this is due to low bone turnover by itself or due to another defect in the calcium buffering ability of bone remains to be established. An increased risk of extraskelatal calcifications due to calcium overload has to be considered in patients with adynamic bone disease⁵⁷.

Evaluation of renal osteodystrophy

The most accurate diagnostic test for determining the type of bone disease associated with chronic kidney disease is bone biopsy with double tetracycline labelling and bone histomorphometric analysis⁵⁸. However, the method is invasive and most centres don't have the expertise in histomorphometry of bone tissue.

In most circumstances clinicians will have to depend upon indirect methods. Plasma PTH levels are still the best available marker of bone turnover at least at high >500 pg/ml and low <100 pg/ml PTH levels, predicting hyperparathyroid bone disease and adynamic bone disease, respectively.

Bone biopsy is, however, recommended in patients with unexplained pathological fractures, in patients with intact PTH levels between 100 and 500 pg/ml and with coexisting conditions such as unexplained hypercalcemia, and severe

bone pain or where aluminium toxicity is suspected.

Bone mineral density measurements are not providing any information on the specific type of renal bone disease, and should be kept to patients with known risk of severe osteoporosis and fractures. Bone radiographs are useful in detecting severe peripheral vascular calcifications.

Prophylaxis and treatment

Prophylaxis and treatment of the secondary HPT and renal osteodystrophy are today directed towards normalizing phosphorus and calcium levels and to control PTH levels, according to the recommended ranges at the different stages of kidney insufficiency. This strategy is stressed by the K/DOQI Guidelines on Bone and Mineral Metabolism⁵⁸ which today are approved by most European and American nephrologists. These guidelines provide a revision of the target ranges for phosphorus, calcium, and PTH and stress the potential complications of previously used strategies. These strategies included extensive use of calcium and calcitriol, leading to an increase in the prevalence of adynamic (low turnover) bone disease which is associated with both increased fractures and vascular calcification^{57,59,60}. Although the K/DOQI Guidelines are based upon the most current knowledge on renal osteodystrophy, they have not yet included a strategy on the use of calcimimetics.

The modern treatment of the secondary HPT and renal osteodystrophy includes: a) restriction of dietary phosphate intake, and treatment with phosphate binders, b) treatment with vitamin D analogs, c) treatment with calcimimetics, d) adequate dialysis therapy, and e) parathyroidectomy.

a) Restriction of dietary phosphate intake and treatment with phosphate binders

Plasma phosphorus levels remain normal until GFR is diminished to less than 25 ml/min, although at the expense of increased PTH secretion. At this stage strategies for reducing the intestinal uptake of phosphorus have to be initiated. Further diminished functioning kidney mass is not able to excrete sufficient amount of phosphorus, phosphorus retention occurs and the degree of hyperphosphatemia intensifies, as GFR further diminishes. Finally at the stage of dialysis, phosphorus is removed only in the dialysate, unfortunately with a clearance which is not sufficient to keep plasma phosphorus levels within the recommended range of 1.1-1.8 mmol/L.

Calcium containing phosphate binders effectively reduce serum phosphorus levels, but provide a huge calcium load, especially when given together with vitamin D analogs. An increased load of calcium together with the elevated phosphorus levels will lead to extraskelletal deposition⁶¹. As such calcium containing phosphate binders should not be provided to dialysis patients who are prone to hypercalcemia and only with caution to those with low levels of PTH.

Sevelamer hydrochloride is a calcium and aluminium free phosphate binder with a phosphate binding capacity similar to that of Ca carbonate and is similar effective controlling hyperphosphatemia^{62,63}. It has been shown that treatment of chronic haemodialysis patients with sevelamer for one year resulted in good control of HPT, less episodes of hypercalcemia, and in diminished cardiovascular calcifications than treatment calcium containing phosphate binders⁶⁴. Recently lanthanum carbonate has been introduced as a new phosphate binder for patients on hemodialysis^{65,66}. Aluminium containing phosphate binders should be avoided.

b) Calcitriol and Vitamin D analogs

As end-stage kidney disease is a condition with vitamin D insufficiency, treatment with biological active vitamin D is logical. Supplementation with vitamin D has documented beneficial effects improving bone metabolism and ameliorating hypocalcaemia and controlling HPT. The therapeutic window is, however, narrow and there is documented risk of developing hypercalcemia, and hyperphosphatemia due to increased intestinal absorption, oversuppression of the parathyroids and of developing adynamic bones and extraskelletal calcifications.

Today there are several biologically active vitamin D analogs beside the genuine hormone, 1,25(OH)₂D₃ (Calcitriol) and its prohormone, 1α(OH)D₃ (Alfacalcidol). Recently a number of so-called “less calcaemic” vitamin D analogs, 22-oxa-1α,25(OH)₂D₃ (Oxacalcitriol), 19-nor-1,25(OH)₂ vitamin D₂ (Paricalcitol), 1α(OH)D₂ (Doxercalciferol), and 26,27-hexafluoro-1,25(OH)₂D₃ (Falecalcitriol) have been approved for clinical use in different countries⁶⁷⁻⁷⁸. The “less calcaemic activity” is, however, still disputed, as such an effect not yet clearly has been demonstrated in the existing clinical studies. Good clinical trials comparing equipotent, in respect to the suppression of PTH levels, doses of the “less calcaemic analogue” and the gold standard, calcitriol, are still missing.

c) Calcimimetics

Calcimimetics act as positive allosteric modulators to increase the sensitivity of the calcium sensing receptor (CaR) on the parathyroid cells to activation by extracellular Ca²⁺⁷⁹. As such, the calcimimetics trick the CaR to “believe” (sense) that the extracellular Ca²⁺ concentration is higher, than it really is. Therefore, PTH secretion is more suppressed in the presence

of a calcimimetic compound, than it otherwise would have been at the actual extracellular Ca^{2+} concentration. Calcimimetics introduced a great step forward in prophylaxis and treatment of secondary HPT and of renal osteodystrophy.

Cinacalcet, Mimpara in Europe or Sensipar in USA, has in several clinical trials clearly been shown to have a dramatic and very rapid suppressive effect on PTH secretion in patients with secondary HPT and even in patients with otherwise refractory HPT⁸⁰. This occurs simultaneously with lowering serum calcium, phosphorus, and the CaxP product⁸⁰. The ability rapidly to suppress PTH secretion without causing hypercalcemia provides a safer, but not necessarily easier way for treatment of secondary HPT. Calcimimetics can be used alone or in combination with vitamin D analogues and phosphate binders. As such treatment with vitamin D analogs will result in a long-term suppression of PTH, while calcimimetics will suppress PTH secretion intermittently allowing the presence of fluctuations of PTH, which theoretically might be of benefit for the potential anabolic effects of PTH on bone⁸¹.

d) Adequate dialysis therapy

The doses and frequency of dialysis have to be sufficient to maintain phosphorus balance. As phosphorus removal is greatest during the initial phase of a haemodialysis session increasing dialysis frequency can provide better control of hyperphosphatemia.

In order to reduce the calcium load a standard dialysate calcium concentration of 1.25 mM is recommended by The K/DOQI Guidelines⁵⁸.

e) Parathyroidectomy (PTX)

PTX should be recommended in patients with severe hyperparathyroidism, with PTH levels

>800 pg/mL, associated with hypercalcemia and/or hyperphosphatemia that are refractory to medical therapy⁵⁸. Effective surgical PTX can be accomplished by subtotal or total parathyroidectomy, with parathyroid tissue autoimplantation. The "hungry bone syndrome" is a severe complication post PTX, which need aggressive treatment of hypocalcaemia.

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