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## Management of Renal Osteodystrophy in Children

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### Introduction

Bone disease in uremia is a consequence of the impaired metabolism of calcium, phosphate, vitamin D and their complex interplay with parathormone (PTH) leading to secondary hyperparathyroidism (SHPT). Retention of phosphorus, decreased levels of calcitriol in blood, decreased levels of serum ionized calcium, reduced numbers of vitamin D receptors and calcium sensors in the parathyroid gland, and skeletal resistance to the calcemic action of PTH play a major role in the development of renal osteodystrophy [1]. Bone resistance to PTH is the principal feature in SHPT and is due to: 7-84 PTH fragments with an inhibitory effect on the action of the whole hormone, a decrease in the density of PTH receptors on osteoblasts and impairment in the recently described RANK-RANKL system with increase in circulating osteoprotegerin levels [2]. It is hypothesized that osteoprotegerin accumulation in uremia might inhibit osteoclastogenesis induced by PTH.

### Histological Spectrum in Renal Osteodystrophy

Data from adult patients point out that histological spectrum of renal osteodystrophy (ROD) has significantly changed and the incidence of adynamic bone disease (ABD) increased due to intensive treatment with 1 $\alpha$ -hydroxylated vitamin D derivatives, use of large doses of calcium salts and peritoneal dialysis. The features of ABD are frequent episodes of hypercalcemia, reduced rate of bone formation and relatively low PTH levels. In children, clinically, besides bone pains and tendency to fractures there is retardation of the growth.

There are scarce data on the histology spectrum of the bone disease in infants and children with chronic renal insufficiency (CRI), on the dialysis and after kidney transplantation. Bone biopsy is considered an invasive technique; in contrast to adult renal units there are only few pediatric centers worldwide with experience in this procedure. In the series of Yalcinkaya et al. [3] the incidence of high turnover bone disease was 47%, followed by low turnover bone disease (29%) and mixed osteodystrophy (24%). The most important conclusion from their study was that the type of ROD depends on the rate of the progression of the renal failure and on the primary disease. Small children with glomerular disease and rapidly progressive course were at high risk for ABD early in the course of disease even under standard therapy with active vitamin D derivatives. In a study from Poland Ziolkowska et al. [4] examined histological types of bone disease in 51 children with end-stage renal failure. ABD was diagnosed in 27%, hyperparathyroidism in 24%, mixed lesion 10%, osteomalacia 2% and normal

histology in 37%. The majority of children with ABD had iPTH levels between 50-150 pg/ml while those with hyperparathyroidism had values above 200 pg/ml. In majority of children with normal histology (69%) iPTH values were between 50-150 pg/ml. When analyzing the group of 17 children with ABD it was found that half of them were treated with alphacalcidol pulses; in 47% of the patients hypercalcemic episodes were observed. Mathias R et al [5] investigated bone biopsy specimen in 21 children and adolescents treated by hemodialysis and found by histomorphometry as follows: osteitis fibrosa, 5; mild hyperparathyroidism, 3; normal histology, 3; aplastic, 6; and mixed lesions, 4. Four of 21 patients were surface positive for aluminum, and seven other patients stained positive for iron in the bone.

Recently a new variant of ABD has been described [6]. Biopsy findings from patients undergoing chronic hemodialysis were reevaluated and it was found that static and dynamic bone forming parameters were similar to that of ABD. The principal difference of this new variant was the presence of increased osteoclastic bone resorption. Since PTH levels were suppressed in this subgroup of patients one may hypothesize that factors other than PTH activate osteoclasts in some patients on chronic hemodialysis (uremic cytokines, toxic metabolites, including beta-microglobulin). Reevaluation of pediatric bone biopsies and analysis of biochemical data may reveal if this variant of ABD is present in this age group and what is its significance for appropriate management.

### Treatment Goals in Children with Renal Osteodystrophy

The treatment goals in children with ROD are to return bone formation toward normal and maintain serum PTH in the range that corresponds to normal rate of skeletal remodeling. Prevention of ROD should start early during the course of chronic renal failure because secondary hyperparathyroidism develops due to relative or absolute deficit in calcitriol and/or calcium. For that purpose phosphate binders and vitamin D sterols are used. There is not still a consensus when to start treatment; some authors prefer phosphate binders while others advocate vitamin D sterols. It seems rational to start treatment when PTH reaches 120 pg/ml, that is a double of the upper normal value (10-65).

Calcium carbonate or acetate is used with the meals (50-100 mg/kg/d). Aluminum containing binders are now used very rarely (<30mg/kg/d) and for short treatment periods. Correction of the acidosis is also essential for CRF patients since it leads to release of the calcium from the bones. So-

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dium- and calcium citrate are avoided since they enhance intestinal aluminum absorption.

Following vitamin D sterols are used: dihydrotachisterol, 25-hydroxvitamin D<sub>3</sub>, 1- $\alpha$ -hydroxvitamin D<sub>3</sub>, 1,25-dihydroxvitamin D<sub>3</sub> (calcitriol). The control of serum Pi is of central importance in prevention ROD since hyperphosphatemia stimulates PTH secretion. Phosphate restricted diet and binders should bring the Pi within the lower normal level for the age. Serum Ca should be regularly monitored in those children receiving calcium salts and calcitriol and the appropriate level will be dependent on the dialysis modality and serum PTH level. In children treated with calcitriol serum PTH > 200 pg/ml and serum Ca < 2.5 mmol/l are 85% sensitive and 100% specific for high-turnover (HTO) bone lesion. In those, whose serum PTH < 150 pg/ml and serum Ca > 2.5 mmol/l there is 100% sensitivity and 92% specificity for adynamic bone disease.

### PTH assays

Determination of the PTH levels is crucial in management of patients with CRF. Levels of PTH often vary in the range between 50-500 pg/ml and this makes difficult the assessment of bone turnover status. Interestingly in few patients with histologically proven low turnover bone disease values of PTH above 400 pg/ml are found. The new third generation assays measure the biologically active whole PTH (1-84). Comparing results using the whole PTH and iPTH assays, the PTH-(7-84) level is indirectly determined and the PTH-(1-84)/PTH-(7-84) ratio can be calculated which is a more accurate indicator of bone turnover [7]. There is enough evidence that PTH (7-84) inhibits calcemic effects of PTH (1-84) and its stimulatory effect on bone turnover.

### Phosphate Binders

A tendency to hypercalcemia and increased incidence of ABD are adverse effects of calcium based phosphate binders, particularly when co-administered with active vit. D derivatives. The newly developed calcium free phosphate binders are sevelamer hydrochloride, lanthanum carbonate and ferric citrate. Of these, there is only limited pediatric experience with sevelamer hydrochloride. In the experimental adenine induced renal failure the animals were treated with sevelamer hydrochloride. Compared with the control group the sevelamer treated rats had lower serum phosphorus, serum CaxPi product, and PTH levels. Moreover, in the treatment group, sevelamer suppressed calcification of the aortic media, and also the osteoid volume, fibrosis volume, and porosity ratio of femurs [8]. The beneficial effect of sevelamer hydrochloride was documented also in clinical studies. The mechanism underlying the slower rate of progression of cardiovascular calcification in sevelamer-treated patients remains uncertain but may relate to decreased calcium loading or to dramatic reductions in LDL cholesterol. Although few side effects were attributed to sevelamer hydrochloride the wider clinical use of this drug is limited by its high price. Treatment with sevelamer hydrochloride should be considered for patients with persistent hypercalcemia during calcium-based binder therapy despite appropriate

adjustment of vitamin D therapy [9]. As previously mentioned pediatric experiences with sevelamer are scarce, at the moment pediatric Renagel study is running.

Other noncalcemic phosphate binders: In the recent report of the international study results on the effectiveness of lanthanum carbonate (Fosrenol) and calcium carbonate on renal bone disease in dialysis patients were presented [10]. The most important finding in this study was that incidence of hypercalcemia in lanthanum carbonate group was very low compared with calcium carbonate group (6% versus 49%). In the lanthanum carbonate group at the end of the trial the percent of patients with abnormal bone histology decreased from 36% to 18%, while in the calcium carbonate group this percent increased from 43% to 53%.

An open-label, random order, crossover comparison study of ferric citrate and calcium carbonate in hemodialysis patients was performed in Taiwan by Yang et al [11]. Ferric citrate (3 g/day) was less effective in decreasing Pi concentration, but did not increase serum Ca concentration. The wider clinical use of both lanthanum carbonate and ferric citrate would depend on the results of the further studies in order to prove safety of these drugs since it is known that both metals accumulate in the bones.

### Hydroxylated Vitamin D Sterols

Calcitriol may be used per os, intravenously or intraperitoneally on daily basis or intermittently as pulse therapy. Calcitriol pulse therapy is suspected to be causally related to hypercalcemia and ABD and reduced growth rate in children with end stage renal failure. Recently, European Study Group on Vitamin D in Children with Renal Failure could not prove that pulse therapy was more effective than daily in controlling SHPT [12]. In a randomized multicenter study the effect of an 8-week course of daily versus intermittent (twice weekly) calcitriol therapy on PTH suppression was studied in 59 children with chronic renal insufficiency (mean Ccr 22.4 $\pm$ 11.6 ml/min per 1.73 m<sup>2</sup>) and secondary hyperparathyroidism. The patients were randomly assigned to treatment with daily oral calcitriol (10 ng/kg per day) or intermittent oral calcitriol (35 ng/kg given twice a week). The investigators concluded that oral calcitriol pulse therapy did not control SHPT more effectively than the daily administration of calcitriol in children with chronic renal failure prior to dialysis.

Oral daily dose of calcitriol (10ng/kg) should be preferred in those children on maintenance dialysis who receive large amounts of calcium salts. If there is tendency to hypercalcemia, dialysate with lower calcium concentration should be used. It is generally accepted that PTH values should be kept 2-3 times higher over the normal range to avoid ABD.

In a recent study from Japan effectiveness and safety of active oral vitamin D derivatives is evaluated in respect of the dose timing [13]. In this study oral D<sub>3</sub> pulses were administered to 13 hemodialysis patients at 08.00 h or 20.00 h for 12 months by a randomized, cross-over design. Mean serum Ca concentration after the trial was 10.92 (95% confidence interval (CI) 10.79, 11.06) and 9.55 mg dl<sup>-1</sup> (95% CI 9.30, 9.71) by 08.00 h and 20.00 h dosing. This study clearly

showed that evening dosing was advantageous in respect to the number of hypercalcemic episodes, stronger PTH suppression and increase in bone mineral density.

### Non-Hypercalcemic Vitamin D Analogues

So-called non-hypercalcemic vitamin D derivatives are 24,25(OH)<sub>2</sub>D<sub>3</sub>, 22-oxa-calcitriol, 19-nor-1,25(OH)<sub>2</sub> vitamin D<sub>3</sub> – paracalcitol, 1 $\alpha$ -(OH) vitamin D<sub>2</sub>. There is favorable clinical experience with Paricalcitol (Zemlar) in adults with chronic renal failure. In a study by Sprague et al [14] paricalcitol was tested versus calcitriol in the treatment of secondary hyperparathyroidism in patients on hemodialysis. Paricalcitol treatment reduced PTH concentrations more rapidly with fewer sustained episodes of hypercalcemia and increased Ca x P product than calcitriol therapy. In a historical cohort study 36-month survival rate was compared among patients undergoing long-term hemodialysis who started to receive treatment with paricalcitol (29,021 patients) or calcitriol (38,378 patients) between 1999 and 2001 [15]. The mortality rate among patients receiving paricalcitol was 3417 per 19,031 person-years (0.180 per person-year), as compared with 6805 per 30,471 person-years (0.223 per person-year) among those receiving calcitriol (P<0.001). A pediatric trial with paricalcitol has recently been completed; release of the data, dosing schedule and approval for use in children is being expected.

### Calcimimetics

In 1993 calcium-sensing receptor (CaR) was discovered and characterized. Soon after that new type of drugs were created, so named calcimimetics, which are agonists of the CaR. The effect is increased sensitivity of the parathyroid gland to extracellular calcium and strong suppression of PTH secretion. In experimental studies as well in humans NPS R-568 showed beneficial effect in respect to PTH suppression. There were few adverse effects; one of these was a mild hypocalcemia. Therefore calcimimetics should be administered in concert with current strategy for management ROD that includes phosphate binders and vitamin D analogues. Yet there is certain concern for the safety of calcimimetics since CaR are distributed in various tissues and effect on their function is not well studied.

### Growth Hormone and Renal Osteodystrophy

It is still controversial if severe osteodystrophy is contraindication for growth hormone treatment in uremia. No significant differences in radiographic osteodystrophy scores, serum calcium, phosphorus, or PTH levels were found between treated and untreated groups [16]. In a Duch study long-term effect of growth hormone were investigated in 45 prepubertal children with chronic renal insufficiency. Growth hormone therapy had no adverse effects on PTH concentration, nor were there any radiological signs of renal osteodystrophy [17]. It is well known from animal models that GH stimulates chondrocyte proliferation. Children with CRF treated with rhGH should be observed for signs of ROD, slipped capital femoral epiphysis, and avascular ne-

crosis with serial radiographs and monitoring serum calcium, phosphorus, alkaline phosphatase, and PTH levels.

### Conclusions

The strategies for prevention and treatment of ROD in children with chronic renal failure should be created on the individual basis. One should consider following factors: age, type of original disease, rate of progression of CRF, nutrition, acidosis, type of dialysis, drugs (corticosteroids, growth hormone etc). The treatment should start very early in the course of renal insufficiency with close monitoring of serum calcium, phosphate, alkaline phosphatase and PTH. The central role has control of serum phosphate and prevention of secondary hyperparathyroidism. Aggressive treatment with calcium based phosphate binders and vitamin D derivatives should be avoided to prevent PTH oversuppression and development of adynamic bone disease.

The expectations of the nephrology community in improving the treatment of ROD are introducing of (i) new calcium and aluminum free phosphate binders; of these there is limited clinical experience with sevelamer hydrochloride (ii) non-hypercalcemic vitamin D analogs (iii) calcimimetics like NPS R-568 which directly stimulate calcium sensing receptor and potently suppresses PTH secretion without increasing plasma calcium.

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