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Management of renal Osteodystrophy in Children

Velibor Tasic MD, PhD

Pediatric Nephrologist, University Children's Hospital, Clinical Center, 17 Vodnjanska, 1000 Skopje, Republic of Macedonia

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Prevention and treatment of renal osteodystrophy (ROD) are great challenges for pediatric nephrologists. The strategies for prevention and treatment of ROD in children with chronic renal failure (CRF) should be created on an individual basis. The following factors should be considered: age, type of primary disease, rate of progression of CRF, nutrition, acidosis, type of dialysis, and 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 parathormone (PTH) levels. Maintenance of serum phosphate within age- appropriate limits is essential for prevention of secondary hyperparathyroidism. PTH levels should be kept within normal limits in predialysis children and 2-3 times over upper normal limit in those on dialysis. Aggressive treatment with calcium-based phosphate binders and vitamin D derivates should be avoided to prevent PTH oversuppression and development of adynamic bone disease. The advantage in this respect is the development of calcium- and aluminum-free phosphate binders, of which there is limited pediatric experience with sevelamer hydrochloride. Paricalcitol is a non-hypercalcemic vitamin D analogue, and preliminary favorable experience has been reported in children. Calcimimetics like cinacalcet hydrochloride, which directly stimulate calcium sensing receptor and potently suppress PTH secretion without increasing plasma calcium in adults, are very promising agents, but pediatric experience is lacking.

Key words: renal osteodystrophy, children, management, hyperparathyroidism, adynamic bone disease.

PATHOPHYSIOLOGY

Renal osteodystrophy (ROD) is a consequence of the impaired metabolism of calcium, phosphate, and vitamin D and their complex interplay with parathormone (PTH), leading to secondary hyperparathyroidism (SHPT). The principal factors involved in development of ROD are retention of phosphorus, decreased levels of calcitriol in blood, decreased levels of serum ionized calcium, and reduced numbers of vitamin D receptors and calcium sensors in the parathyroid gland.[1, 2] Hyperphosphatemia is associated with hypocalcemia and inhibition of the enzyme 1-alpha hydroxylase. Hyperphosphatemia per se is a strong stimulus for secretion of PTH from the parathyroid glands. The mechanism of direct action of the phosphorus on the parathyroid glands is unclear, but it is very likely that there is a phosphate sensor located in the cell membranes in the parathyroids. Impaired synthesis of calcitriol, even in mild chronic insufficiency, leads to a decrease in intestinal calcium absorption and hypocalcemia. Calcitriol affects the parathyroid gland through its action on the vitamin D receptors, while calcium acts through calcium sensing receptors. Reduced levels of both serum calcitriol and calcium are responsible for development of SHPT. Skeletal resistance to the calcemic action of PTH also plays an important role in the development of ROD[3]. This resistance is due to (i) 7-84 PTH fragments which have an inhibitory effect on the action of the whole hormone (ii) decrease in the density of PTH receptors on osteoblasts and (iii) impairment in the recently described RANK-RANKL system with increase in circulating osteoprotegerin levels[4]. It is believed that the accumulation of osteoprotegerin in uremia might inhibit osteoclastogenesis induced by PTH.

BONE BIOPSY AND HISTOLOGICAL SPECTRUM IN ROD

Bone biopsy is the gold standard for assessment of ROD. This technique is considered invasive in children and only a few pediatric centers worldwide are familiar with this procedure. Accumulated data from adult studies point out that the histological spectrum of ROD has significantly changed in the last two decades. Introduction of hydroxylated vitamin D derivates, the use of large doses of calcium salts and peritoneal dialysis are responsible for increased incidence of adynamic bone disease (ABD). The principal features of ABD are frequent episodes of hypercalcemia, reduced rate of bone formation and relatively low PTH levels. In children, clinically, in addition to bone pain and tendency to fractures, there is retardation of the linear growth.

There are only a few studies evaluating the histology spectrum of the bone disease in infants and children with chronic renal insufficiency (CRI) on dialysis and after kidney transplantation. Yalcinkaya *et al.*[5] found in their series that the incidence of high turnover bone disease was 47%, followed by low turnover bone disease (29%) and mixed osteodystrophy (24%). The authors concluded that the primary disease and the rate of the progression of the renal failure influenced the type of ROD. Thus, small children and those with glomerular disease and rapidly progressive course were at high risk for ABD. Ziolkowska *et al.* [6] in their study evaluated a series of 51 children with end-stage renal failure and diagnosed ABD in 27%, hyperparathyroidism in 24%, mixed lesion in 10%, osteomalacia in 2% and normal histology in 37%. The majority of children with ABD had PTH levels between 50-150 pg/ml, while those with hyperparathyroidism had values above 200 pg/ml. In the majority of children with normal histology (69%), PTH values were between 50-150 pg/ml. Analysis of 17 children with ABD showed that half of them were treated with alpha-calcidiol pulses and had frequent hypercalcemic episodes. Mathias *et al.*[7] investigated by histomorphometry bone biopsy specimens in 21 children and adolescents treated by hemodialysis and reported the following: osteitis fibrosa, 5; mild hyperparathyroidism, 3; normal histology, 3; and aplastic (6) and mixed (4) lesions. Four of 21 patients were surface-positive for aluminum, and seven other patients stained positive for iron in the bone.

A new variant of ABD has been described in patients undergoing chronic hemodialysis[8]. It was found that static and dynamic bone forming parameters were similar to that of ABD, but there was 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, and 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 as well as its significance for appropriate management.

TREATMENT STRATEGY IN CHILDREN WITH RENAL OSTEODYSTROPHY

Prevention and treatment of ROD are great challenges for pediatric nephrologists. The strategy is created on an individual basis, bearing in mind the current biochemical status and the level of the renal function. The principal aim in children with ROD is to return bone formation toward normal and to optimize the serum PTH in the range that corresponds with a normal rate of skeletal remodeling. There is still no consensus regarding when and how to start treatment; some authors prefer phosphate binders while others advocate vitamin D sterols. It seems rational to start treatment when PTH exceeds the upper normal limit (UNL), 10-65 pg/ml.

Maintenance of the serum phosphorus within the lower to mid normal values for age is essential for prevention of ROD since hyperphosphatemia stimulates PTH secretion. For this purpose, dietary phosphorus intake should be reduced by appropriate diet, but this is difficult to realize due to the concurrent reduction in protein intake that is very important for the growing organism. With current dialysis techniques, phosphorus removal is insufficient, thus intestinal phosphorus absorption should be blocked by the use of phosphate binders. Calcium carbonate or acetate is used with meals (50-100 mg/kg/d). Due to its toxicity, aluminum-containing phosphate binders are now used very rarely and for short treatment periods. Correction of the acidosis is also essential for chronic renal failure (CRF) patients, since it leads to release of calcium from the bones. Sodium- and calcium citrate are avoided since they enhance intestinal aluminum absorption.

The following vitamin D sterols are used: dihydrotachysterol, 25-hydroxyvitamin D3, 1-alpha-hydroxyvitamin D3, and 1,25-dihydroxyvitamin D3 (calcitriol). Serum calcium (Ca) should be regularly monitored in those children receiving calcium salts and calcitriol, and the appropriate level will depend 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 with serum PTH < 150 pg/ml and serum Ca >2.5 mmol/L, there is 100% sensitivity and 92% specificity for ABD.[9] The generally accepted attitude is to keep serum PTH 2-4 times higher than UNL in children on dialysis and up to 2 times UNL in pre-dialysis cases. The recently published data from the Nephro-Urology unit at the Great Ormond Street Hospital, London are very intriguing.[10, 11] The policy of this unit is to maintain PTH levels within a normal range to the extent possible throughout the course of CRI into terminal renal failure in order to prevent SHPT and escape of parathyroid glands from normal control mechanisms. The results of this retrospective study showed that catch-up growth occurred despite normal PTH values and this fact does not support the risk for development of ABD, which clinically manifests in children with pains, bone fractures and growth retardation.[10] The great disadvantage of this study is the lack of bone biopsies to confirm this interesting clinical observation.

PTH ASSAYS

Determination of the PTH levels is crucial in management of patients with CRF. Levels of PTH often vary between 50-500 pg/ml and this makes assessment of bone turnover status difficult. Interestingly, in a few patients with histologically proven low turnover bone disease, PTH values above 400 pg/ml have been found. The new third generation assay measures the biologically active whole PTH (1-84)[11, 12]. 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[12,13]. There is enough evidence that PTH (7-84) inhibits calcemic effects of PTH(1-84) and its stimulatory effect on bone turnover.

PHOSPHATE BINDERS

Development of ABD and episodes of hypercalcemia are consequences of the use of calcium- based phosphate binders, which are often used in large doses to control hyperphosphatemia, particularly when co-administered with active vitamin D derivates. This leads to increase of the CaxPi ion product and development of vascular and soft tissue calcification. Analyzing 120 autopsies of children with renal failure, Milliner *et al.*[14] found soft tissue calcifications in 60% of the patients and systemic calcinosis in 36%. The progress in this respect was achieved via the development of new calcium- and aluminum-free phosphate binders: sevelamer hydrochloride, lanthanum carbonate and ferric citrate. Of these, there is only limited pediatric experience with sevelamer hydrochloride. In the experimental study, animals treated with sevelamer showed lower serum phosphorus, serum CaxPi product, and PTH levels. Sevelamer suppressed calcification of the aorta media, and also the osteoid volume, fibrosis volume, and porosity ratio of femurs.[15] The beneficial effect of sevelamer hydrochloride on vascular calcification was also documented 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 low density lipoprotein (LDL) cholesterol.

As previously mentioned, pediatric experiences with sevelamer are scarce; recently Mahdavi *et al.*[16] reported their experience from an open label study in which sevelamer was administered in 17 children undergoing hemodialysis (n=3) or peritoneal dialysis (14). After the two-week washout period, the children were given sevelamer for six months, and the analysis showed a significant decrease in serum phosphate concentration and CaxPi product, whereas the serum Ca levels remained unchanged. Serum levels of the bicarbonate did not change in this study, as previously reported in adult patients undergoing hemodialysis. No effect was observed concerning the lipid status, which was in contrast to reports from adult studies; this may be explained by the smaller size of the studied group and the shorter observational period.

The current formulations of sevelamer (capsules and tablets) are inappropriate for infants because the hydrogel formed a viscous

solution that infants were unable or unwilling to swallow. Ferrara *et al.*[17] pretreated fresh or frozen breast milk with sevelamer; within 10 minutes hydrogel settled at the bottom of the container enabling the supernatant to be easily decanted. In this way the phosphorus content decreased by 78% without significant changes in other macronutrients or electrolytes.

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[18].

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[19]. The incidence of hypercalcemia in the lanthanum carbonate group was very low (6% versus 49%). An important finding was that at the end of the trial, the percentage of patients with abnormal bone histology in the lanthanum carbonate group decreased from 36% to 18%, while this percentage increased in the calcium carbonate group from 43% to 53%.

Yang *et al.* [20] compared ferric citrate and calcium carbonate in hemodialysis patients, and found that ferric citrate (3 g/day) was less effective in decreasing Pi concentration, but did not increase serum Ca concentration. The safety of both drugs should be fully proven before wider clinical use, since it is known that both metals accumulate in the bones.

HYDROXYLATED VITAMIN D STEROLS

Calcitriol, the most commonly used hydroxylated vitamin D sterol, may be administered per os, intravenously or intraperitoneally - on a daily basis or intermittently as pulse therapy. Calcitriol pulse therapy is suspected to be causally related to hypercalcemia and ABD and to reduced growth rate in children with end-stage renal failure. The European Study Group on Vitamin D in Children with Renal Failure could not prove that pulse therapy was more effective than daily therapy in controlling SHPT[21]. In a randomized multicenter study, the effect of an eight-week course of daily (10 ng/kg per day) versus intermittent (35 ng/kg given twice weekly) calcitriol therapy on PTH suppression was studied in 59 children with CRI (mean Ccr 22.4±11.6 ml/min per 1.73 m^2). The investigators concluded that oral calcitriol pulse therapy did not control SHPT more effectively than the daily administration of calcitriol in children with CRF prior to dialysis.

An oral daily dose of calcitriol (10 ng/kg) should be preferred in those children on maintenance dialysis who receive large amounts of Ca salts. If there is tendency to hypercalcemia, dialysate with lower Ca 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 derivates were evaluated with respect to the dose timing[22]. In this study, oral D3 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 (95% CI 9.30, 9.71) by 08.00 h and 20.00 h dosing, respectively. This study clearly showed that evening dosing was advantageous with respect to the number of hypercalcemic episodes, stronger PTH suppression and increase in bone mineral density. Similar beneficial effects in reducing the frequency of hypercalcemic episodes with evening dosing of calcitriol were reported by Shaefer *et al.*[23] and Moe *et al.*[24] It is well known that serum Ca levels follow a diurnal rhythm, with highest concentrations during the morning and lowest during the night, thus administration of calcitriol in the evening hours produces less hypercalcemic episodes[25].

NEW VITAMIN D ANALOGUES

Vitamin D therapy with calcitriol or alpha-calcidiol is effective in suppressing the PTH secretion from the parathyroids, but the adverse effects, such as frequent episodes of hypercalcemia, hyperphosphatemia and increased CaxPi product, are significant. Great hope was generated with development of less hypercalcemic vitamin D derivates, of which only three have been used in clinical practice: 22-oxa-calcitriol (Maxacalcitol), paricalcitol (Zemplar) and doxecalciferol (Hectorol)[26].

Favorable clinical experience with paricalcitol (Zemplar) was reported in adults with CRF. Sprague *et al.*[27] tested paricalcitol versus calcitriol in patients on hemodialysis and found that paricalcitol reduced PTH concentrations more rapidly with fewer sustained episodes of hypercalcemia and with less of an increase in CaxPi product than observed with calcitriol therapy. In a large retrospective study, a 36-month survival rate was compared among hemodialysis patients who started to receive treatment with paricalcitol (29,021 patients) versus calcitriol (38,378 patients) between 1999 and 2001.[28] The mortality rate was lower in the paricalcitol group (0.180 vs. 0.223 per person-year; $P<0.001$). There is only one pediatric study reported in an abstract form[29], which showed that intravenous paricalcitol was effective and well tolerated for treatment of SHPT. Preliminary results with a new formulation of paricalcitol (capsules) have also been reported; this is particularly important for predialysis children and those treated with peritoneal dialysis[30].

CALCIMIMETICS

In 1993, calcium-sensing receptor (CaSR) was discovered and characterized. Soon thereafter, a new type of drug was created, termed calcimimetics, which are agonists of the CaSR. These drugs are small organic molecules that lower the threshold for CaSR activation by extracellular calcium ions. The effect is suppression of PTH secretion, which ensues within minutes after administration of the drug. In experimental studies, as well as in humans, calcimimetics showed suppression of PTH secretion without an increase in serum Ca, phosphorus or CaxPi product[30,31]. Therefore, calcimimetics should be administered in concert with the current strategy for management of ROD that includes phosphate binders and vitamin D analogues. There were few adverse effects, one of which was a mild hypocalcemia. A favorable experience was accumulated from clinical studies in adults using AMG-073, whose generic name is cinacalcet hydrochloride[31,32,33,34,35]. The drug has not been evaluated in patients younger than 18 years[31]. There is certain concern regarding the safety of calcimimetics, since CaSRs are distributed in various tissues and effect on their function is not well studied. This is important for the skeleton in growing children, since CaSRs are expressed in the epiphyseal growth plate chondrocytes. The role of CaSR in chondrocyte proliferation and differentiation is not yet known.

GROWTH HORMONE AND RENAL OSTEODYSTROPHY

Administration of growth hormone in uremic children is still controversial. No significant differences in radiographic osteodystrophy scores, and serum Ca, phosphorus, or PTH levels were found between treated and untreated groups[36]. Long-term effects of growth hormone were investigated in 45 prepubertal Dutch children with CRI[37]. No adverse effects related to PTH concentration or development of radiological signs of ROD were reported in this study[37]. It is well known from animal models that growth hormone stimulates chondrocyte proliferation. Children with CRF receiving growth hormone should be regularly observed for signs of ROD and slipped capital femoral epiphysis and avascular necrosis on serial radiographs, and serum Ca, phosphorus, alkaline phosphatase, and PTH levels should be monitored.

PARATHYROIDECTOMY

Parathyroidectomy (PTX) is now rarely indicated due to better medical control of SHPT. Current indications for PTX are severe episodes of hypercalcemia and hyperphosphatemia with high levels of circulating PTH unresponsive to intensified medical therapy, severe bone disease with recurrent fractures, extraskeletal calcifications and calciphylaxis[2]. Prior to PTX, bone biopsy should be performed to exclude aluminum-related bone disease that may worsen after PTX. Surgical extirpation is preferred over ethanol injections into the glands.

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