Abstract  Childhood renal osteodystrophy (ROD) is the consequence of disturbances of the calcium-regulating hormones vitamin D and parathyroid hormone (PTH) as well as of the somatotroph hormone axis associated with local modulation of bone and growth cartilage function. The resulting growth retardation and the potentially rapid onset of ROD in children are different from ROD in adults. The biochemical changes of ROD as well as its prevention and treatment affect calcium and phosphorus homeostasis and are directly associated with the development of cardiovascular disease in pediatric renal patients. The aims of the clinical and biochemical surveillance of pediatric patients with CRF or on dialysis are prevention of hyperphosphatemia, avoidance of hypercalcemia and keeping the calcium phosphorus product below 5 mmol²/l². The PTH levels should be within the normal range in chronic renal failure (CRF) and up to 2–3 times the upper limit of normal levels in dialysed children. Prevention of ROD is expected to result in improved growth and less vascular calcification.

Keywords  Chronic renal failure · Secondary hyperparathyroidism · Calcium-phosphate product · Vitamin D · Parathyroidectomy

Introduction

Chronic renal failure is associated with specific abnormalities of skeletal homeostasis, commonly called renal osteodystrophy (ROD), which if not treated appropriately during the critical phases of skeletal growth can result in bone deformities and a disturbed growth pattern. The main factors for the development of ROD are disturbances in the calcium phosphate homeostasis, in vitamin D and parathyroid hormone metabolism as well as alterations in the somatotroph axis, i.e., on the endocrine and paracrine levels. In recent years it has been recognized that the spectrum of renal bone disease covers ‘high-’ as
well as ‘low-turnover’ conditions. As a consequence of chronic renal failure itself and of the treatment of renal bone disease, high plasma phosphate levels and an elevated calcium phosphorus product are common. These are important risk factors for the development of vascular calcification and cardiovascular morbidity and mortality in young adults who have been on renal replacement therapy since childhood [1, 2]. Because aluminium-containing phosphate binders are no longer indicated in children, aluminium-related osteopathy is not considered in these recommendations.

The European Pediatric Peritoneal Working Group (EPPWG) was established in 1999 by pediatric nephrologists with a major interest in peritoneal dialysis and has, among others, published guidelines on chronic and acute peritoneal dialysis [3, 4, 5, 6]. The group incorporates pediatric nephrologists from 12 European countries. One of the functions of the group is to establish expert guidance in important clinical areas associated with chronic renal failure and dialysis [now the European Pediatric Dialysis Working Group (EPDWG)] in conjunction with other members of the multidisciplinary team. These guidelines were initiated and discussed at meetings of the group and developed by e-mail discussion to develop consensus of opinion based upon cumulative clinical experience and reported studies.

**Recommendations**

**Recommendation 1**

**Clinical, biochemical and radiological markers of renal bone disease should be monitored regularly.** The clinical markers of renal bone disease to be prevented are signs of overt rickets, slipped femoral epiphysis and disturbances of growth. The biochemical markers are plasma phosphate, calcium, alkaline phosphatase, bicarbonate and intact parathyroid hormone (PTH). The minimal frequency of measurements (and target ranges) for biochemical markers in a stable phase vary according to renal function (Table 1). If the patient has active ROD, additional blood samples may be required.

Plasma calcium must be adjusted for albumin levels (= corrected calcium) or by measuring ionized (free) calcium, in patients with hypoalbuminemia or acid-base disorders. Ionized calcium values are often available on blood gas analysis systems with calcium-sensitive electrodes, but correct values are only obtained in validated conditions. Alkaline phosphatase as a marker for osteoblast activity has particular importance in both low and high-turnover bone disease with elevated or low alkaline phosphatase serum levels, respectively.

**Table 1** Frequency of measurements for biochemical and radiological markers of renal osteodystrophy

| Marker | Frequency of measurement (every x month) | Target |
|--------|----------------------------------------|--------|
| Calcium or Ionized calcium | GFR 59–30 6 3 1 | Normal range (corrected calcium)² |
| Phosphate | GFR 29–15 6 3 1 | Normal range² |
| Calcium phosphorus product | GFR <15, dialysis (Evidence) 6 3 1 | Normal range for age band |
| Alkaline phosphatase | GFR <15, dialysis (Evidence) 6 3 1 | ≤5.0 mmol²/l² |
| Serum bicarbonate/base excess | GFR <15, dialysis (Evidence) 6 3 1 | Target range 3.3–4.4 mmol²/l²³ |
| Intact PTH/whole PTH | GFR <15, dialysis (Evidence) 6 3 1 | Normal range for age band |
| Alkaline phosphatase | GFR <15, dialysis (Evidence) 6 3 1 | Normal range, at least: bicarbonate >22 mmol/l |
| Serum bicarbonate/base excess | GFR <15, dialysis (Evidence) 6 3 1 | Base excess >–5 mmol/l |
| Intact PTH/whole PTH | GFR <15, dialysis (Evidence) 6 3 1 | Normal range in moderate CRF (GFR >29 ml/min/1.73m²) |
| 25-(OH) vitamin D₃ | As indicated⁴ | Up to 2–3 times upper limit of normal in advanced CRF or on dialysis |
| Left hand and wrist X-ray | As indicated⁴ | >20 ng/l |

Cortical and trabecular bone.

Normal range (corrected calcium)²
Normal range²
Target range 3.3–4.4 mmol²/l²³
Normal range for age band
Normal range, at least: bicarbonate >22 mmol/l
Base excess >–5 mmol/l
Normal range in moderate CRF (GFR >29 ml/min/1.73m²)
Up to 2–3 times upper limit of normal in advanced CRF or on dialysis
>20 ng/l
No radiological signs of hyperparathyroidism
No Looser zones or osteopenia

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Radiological signs of renal bone disease, which alone are not sensitive enough to indicate therapy-adaptations, include signs of hyperparathyroidism and growth zone lesions. Periosteal resorption zones and metaphyseal changes are the most obvious signs. In late adolescent and young adult patients, Looser zones as specific signs of osteomalacia may be found. The sites and expression of bone lesions are age-dependent according to the age-dependent growth and remodeling at different sites of the skeleton. In pre-school children, the metaphysis of the distal radius and ulna may present only minor abnormalities, whereas more severe lesions may be seen at the upper and lower femoral epiphysis. A dynamic bone disease shows no specific radiological changes. However, extraosseous calcifications, fractures or osteopenia may indicate dynamic bone disease.

Histological evaluation of bone biopsy specimens remain the “gold standard” in assessment of renal osteodystrophy. However, due to its invasive nature, bone biopsies are not performed in clinical practice, but they remain an important tool for research [12].

Recommendation 2

**Metabolic acidosis should be corrected (evidence).** Chronic metabolic acidosis leads to increased bone resorption and inhibits endochondral bone formation in animal experiments [13, 14]. Infants with isolated chronic metabolic acidosis show growth retardation [14]. In adult hemodialysis patients, negative aspects of chronic metabolic acidosis on metabolism have been reported [15]. Therefore, metabolic acidosis should be corrected by a stepwise approach: The first step is optimization of the dialysis regimen both for HD- and PD-patients [4, 15]. Since the introduction of HCO₃-based PD solutions [16], metabolic acidosis is a less frequent problem. In combination with a daytime-dwell, patients may even be at risk for alkalosis [17]. However, if these adaptations do not result in correction of the metabolic acidosis, sodium bicarbonate should be administered orally. Whenever possible, formulations that dissolve in the small intestine should be used. The use of sodium citrate increases the risk of aluminium absorption [18, 19]. Acidosis should be corrected to the normal range of the local laboratory.

Recommendation 3

**The plasma-phosphate level should be kept within the normal age-specific range (evidence).** In children with chronic renal failure, hyperphosphatemia is observed at GFR levels below 40 ml/min/1.73m² [20] and almost always in children on dialysis. Hyperphosphatemia has several deleterious effects on PTH secretion [21, 22], parathyroid cell proliferation [23] and soft tissue (vascular) calcification [1, 2].

Increased phosphate levels stimulate PTH secretion in vitro [24] and in vivo [21, 25] independent of calcium and 1,25(OH)₂ vitamin D₃ levels. This effect of phosphate on PTH secretion occurs via post-transcriptional processes by regulating pre-pro-PTH mRNA stability [26]. Furthermore, a reduction of serum-phosphate results in a parallel reduction of PTH levels without change in serum calcium [27]. Hyperphosphatemia accelerates parathyroid cell proliferation [23], which can result in nodular hyperplasia and severe hyperparathyroid bone disease necessitating parathyroidectomy (see below).

Increased plasma phosphate levels have a profound effect on soft tissue and vascular calcification, which are often observed in young patients on or even after dialysis [1, 2, 28], increasing the risk of cardiovascular morbidity and mortality. Block et al. [29] found an increased risk of death for serum phosphate exceeding 2.09 mmol/l in adult patients; other studies described a much lower phosphate level (~1.4–1.6 mmol/l) at which a higher incidence of calcifications was found [1, 30, 31]. The histology of the calcification pattern is quite distinct from the process of atherosclerosis. In renal patients, extensive calcification of the tunica media occurs even after short periods of dialysis, as shown by investigations of the epigastric artery in adult patients [32]. Experimental work gave evidence for an active role of phosphate in this process as phosphate induces osteoblastic marker followed by calcification in cultured smooth muscle cells [33]. Dialysis patients are at risk of heart failure. Although this is a multifactorial process, it was demonstrated in animal experiments that high plasma phosphate levels per se accelerated cardiac fibrosis [34].

Recommendation 4

**If plasma phosphate is elevated, phosphate intake should be limited to the recommended levels.** Dietary intake of protein and as a consequence of phosphate in western countries usually exceeds the recommended intake at least in adolescent dialysis patients. Therefore, dietary counseling should be performed by a trained dietitian [35]. If the dietary record shows a protein intake above the recommended level for pediatric dialysis patients, the patients and their parents should be trained to reduce their phosphate intake. This may start with the reduction of dairy products and/or substitution with special low-phosphorus products and a reduction of meat intake.

Recommendation 5

**In case of hyperphosphatemia, the dialysis efficacy should be optimized (evidence).** Phosphate is slowly transported via the peritoneal membrane into the dialysate [36]. The dialysate to plasma ratio (D/P) for phosphate is volume and time related; after 4 h in standard peritoneal equilibration tests, this ratio reaches the value of 0.5–0.6, which is a much lower ratio than for urea, which is usually nearly 1. Therefore, an increase in phosphate removal
should consider not only an increase in dwell volume to 1,000–1,400 ml/m² BSA, but also dwell time optimization, avoiding a too short dwell time. A daytime dwell should be added. The details of a dialysis regimen optimization has been described elsewhere [5]. However, due to the low clearance of phosphate achievable even with an optimized PD regimen, dietary phosphate restriction and the use of oral phosphate binders are almost always necessary.

The dialytic phosphate removal kinetic during a hemodialysis session differs from urea kinetic: after an early initial drop the phosphatemia decrease only slowly [37, 38]. Therefore, it is admitted that the hemodialysis phosphate purification capacity is directly impacted by the duration of the dialysis session, because the phosphate shift from the intracellular to the vascular compartment is time-dependent. Therefore, longer dialysis sessions [39] or daily dialysis sessions [40, 41, 42] offer a unique, powerful dialysis method for optimal phosphate purification. The hemodialysis modality, HD, HF or HDF, and the type of the synthetic membrane used have only a limited impact on dialytic phosphate removal [38], whereas the dialysate composition in terms of glucose and bicarbonate concentration are presumed to be of importance [42, 43, 44], modulating a shift of intracellular phosphate trapped in the cells, where it is not available for dialysis exchanges.

Recommendation 6

For control of hyperphosphatemia, aluminium-free phosphate binders should be administered (evidence).

Phosphate binders are necessary to reduce phosphate absorption from the gut. Ca-containing phosphate binders, i.e., calcium carbonate (CaCO₃, elemental calcium content 40%) or calcium acetate (CaAc, elemental calcium content 25%) should be used as the first line. No data are published on the efficacy and safety of calcium acetate/magnesium carbonate compound phosphate binders in pediatric patients. The upper intake level of elemental calcium is suggested to be 2,500 mg/day for healthy children above 4 years of age [19]. Whereas for adult dialysis patients the DOQI guidelines suggest to limit the elemental calcium intake to 2,000 mg/day, no safe upper level can be given for the pediatric age band. However, a positive calcium balance in the range of +200–+300 mg in the growing skeleton should be maintained. In contrast, a too high calcium load should be avoided, because one of the identified risk factors for soft tissue calcification in pediatric CRI patients was cumulative calcium intake [2, 24].

Calcium-containing phosphate binders are started at approximately 500 mg per 200 mg phosphate content of the diet (0–1 years, 1–2×500 mg; 1–4 years, 2–3×500 mg/day; 5–8 years, 3–4×500 mg/day; 9–18 years, 5×500 mg). An alternative approach is a start dose of approximately 50 mg/kg/day, which is well below the doses given in clinical studies. Phosphate binders are then adjusted to normalize serum-phosphate and calcium. CaCO₃ can be crushed to fine powder, or a 10% solution can be used for administration in infants, often via a feeding tube. The phosphate binders should be taken with meals, because fecal excretion of phosphate was higher when calcium acetate was given with meals instead of in between meals [45]. Biochemically, CaAc has a higher phosphate binding capacity, which is independent of the pH. The higher efficacy of CaAc, calculated on a weight basis compared to CaCO₃, for phosphate control was also shown in clinical practice in adult and pediatric patients [46, 47].

Recommendation 7

Vitamin D deficiency should be avoided (evidence). In early renal failure, an increase of PTH correlates positively with 25(OH)-vitamin D₃ levels [51]. Renal synthesis of 1,25(OH)₂D₃ is impaired in chronic renal dis-
25-OH-vitamin D3, but not 1,25(OH) 2 D3, improved decreased PTH serum concentrations [53]. Furthermore, because 1,25(OH)2 vitamin D 3 directly inhibits osteo-
therapy with high-dose active vitamin D metabolites, phosphatase are almost always associated with high-turnover normal or high serum calcium and high alkaline phos-
(>four times the upper normal range) in the presence of disease (evidence).

Normal or high levels of PTH are reported to be associated with a normal ratio of intact PTH to “whole” PTH and normal levels of alkaline phosphatase, indicat-
ing a physiological PTH secretion and unremarkable bone turnover [10]. In such patients, slight catch-up growth with PTH levels at the upper limit of normal was reported [56]. In a sub-group analysis, improved growth was re-\nstricted to patients with enteral feeding tubes.

Recommendation 8
Marked hyperparathyroidism should be prevented in children with CRF prior to dialysis (evidence). Due to the risk of persisting bone disease and the development of parathyroid adenoma, an increase in PTH above normal to slightly elevated levels should be prevented in children with CRF. Therefore, low doses of active vitamin D metabolites should be given in time. In adult patients this treatment regimen has resulted in controlled iPTH without negative aspects [55]. In children with moderate renal failure (GFR >30 ml/min/1.73 m²), normal levels of PTH in association with strictly controlled phosphate levels are associated with a normal ratio of intact PTH to “whole” PTH and normal levels of alkaline phosphatase, indicat-
ing a physiological PTH secretion and unremarkable bone turnover [10]. In such patients, slight catch-up growth with PTH levels at the upper limit of normal was reported [56]. In a sub-group analysis, improved growth was re-
stricted to patients with enteral feeding tubes.

Recommendation 9
PTH levels should be kept at two to three times the upper limit of the normal range in end-stage renal disease (evidence). Grossly elevated PTH concentrations (>four times the upper normal range) in the presence of normal or high serum calcium and high alkaline phosphatase are almost always associated with high-turnover bone disease [56, 57]. The exception is intermittent therapy with high-dose active vitamin D metabolites, because 1,25(OH) 2 vitamin D 3 directly inhibits osteo-
blast function and proliferation. Hyperphosphatemia can occur in hyperparathyroid bone disease because of ex-
cessive bone resorption.

However, in pediatric dialysis patients low and even normal levels of PTH are reported to be associated with low turnover bone disease [57]. A PTH concentration higher than in healthy subjects is needed to stimulate bone turnover due to resistance of the skeleton to PTH in advanced renal failure. If PTH falls into the (low) normal range, the risk of hypercalcemia increases [58]. Hyper-
phosphatemia and hypercalcemia can develop in low turnover bone disease because the skeleton is unable to take up enough phosphate and calcium. Low bone turn-
over or adynamic bone disease is increasingly observed in adult [59] as well as in pediatric PD patients [56]. Risk factors for adynamic bone disease are high calcium intake (Ca-containing phosphate binders), therapy with high doses of active vitamin D metabolites, peritoneal dialysis using dialysis fluid with high calcium content and age (adolescents after the growth spurt). Biochemically, hyper-
calcemia and/or PTH levels within or below the normal range are indicative of low turnover bone disease [56, 58], which may adversely affect growth in dialysed children [60]. Therefore, active vitamin D therapy should be reduced or stopped if PTH falls below the low normal range [57, 59, 61]. If PTH remains below normal despite normal calcium and phosphate levels, the dialysate should be changed to low calcium solutions (1.0 or 1.25 mmol/l) to stimulate PTH secretion [61], if this is not already used as the standard solution [5].

Recommendation 10
If PTH is elevated in children with CRF or if PTH is elevated more than two to three times normal in the presence of Pi <2 mmol/l in dialyzed children, active vitamin D metabolites should be administered orally (evidence). Treatment with active vitamin D metabolites results in biochemical and/or histological improvement in patients with high-turnover bone disease. Doses of 1,25(OH)2 vitamin D 3 or 1α-(OH) vitamin D 3 usually range from 0.1 µg/day to 0.75 µg/day, with a starting dose of 20–40 ng/kg. High doses often induce hypercalcemia, necessitating the reduction or discontinuation of vitamin D therapy (see hypercalcemia).

As to the mode of administration of the active vitamin D metabolites, intravenous or oral therapy, have the same efficacy [63]. Therefore, the oral route should be pre-
ferred in children on dialysis. Doses should be given in the evening, because fewer episodes of hypercalcemia have been reported compared to taking the vitamin D metabolites in the morning [64]. Intermittent therapy was shown to be effective to suppress elevated PTH serum levels [59]. However, recent data indicate that large in-
termittent 1,25(OH) 2 vitamin D 3 doses adversely affect bone turnover [57, 61, 65] and chondrocyte activity [66] resulting in low turnover bone disease and in reduced growth [65, 66, 67, 68]. In addition, episodes of hyper-
calcemia occur with similar frequency with the intermit-
tent or oral administration of vitamin D metabolites [63, 69]; furthermore, the intermittent mode of administration was not shown to be more effective in suppressing PTH levels in adult [70] and pediatric [63] patients in prospective, randomized trials. For the above mentioned reasons, intermittent high-dose vitamin D therapy should be avoided in pediatric patients.

Three newer vitamin D analogs, so called “non-hy-
percalcemic” vitamin D analogs (doxercalciferol, pari-
calcitol and 22-oxa-calciferol), have been introduced in clinical use in adult patients with secondary hyperpara-
thyroidism due to CRF. Despite their ability to induce less hypercalcemia in animal experiments, only one clinical
study with a head-to-head comparison of the new vitamin D analogue (paricalcitol) is available demonstrating a borderline reduction of hypercalcemia or a decrease in calcium phosphorus product [71]. No data are available for their use in children.

Agents that specifically enhance the sensitivity of the calcium-sensing receptor, called calcimimetics, used in combination with active vitamin D metabolites in adult dialysis patients resulted in a persistent decrease of PTH levels without elevated calcium phosphorus product [72]. If plasma Ca or Pi is high in the presence of elevated PTH, the calcimimetics may become first choice. However, no data for pediatric patients are available.

**Recommendation 11**

**Treatment with growth hormone should not be started in the presence of severe hyperparathyroid bone disease.** It is well established that the uremic growth retardation is at least in part due to disturbed pulsatile secretion of growth hormone as well as a peripheral growth hormone resistance [73]. After correction of metabolic acidosis and normalization of caloric intake, administration of recombinant human growth hormone increases growth velocity resulting in catch-up growth and in improved final height [74]. Growth hormone directly stimulates growth cartilage proliferation and metabolism and osteoblast activity [75, 76]. This growth promoting effect of GH was suspected to increase the metaphyseal instability induced by severe hyperparathyroidism. In hyperparathyroid bone disease, i.e., osteitis fibrosa, a fibrous layer is formed at the metaphyseal junction of the growth plate with the bone tissue. This can lead to epiphyseal slipping resulting in gross deformities of the affected long bones [77]. Therefore, parathyroid hormone, as well as calcium and phosphate levels, should be treated towards the recommended normal ranges prior to administration of GH. However, in a recent prospective study, no increased frequency of epiphyseal slipping associated with the use of growth hormone was reported [78]. After the start of GH administration, an increase of PTH levels was observed [79, 80].

**Recommendation 12**

**In case of hypercalcemia, active vitamin D metabolites and calcium-containing phosphate binders should be stopped and dialysate changed to low calcium solutions (evidence).** Hypercalcemia and elevated calcium phosphorus product (>5.0 mmol²/l²) should be corrected promptly (Fig. 1). Vitamin D metabolites should be discontinued and in case of persisting hypercalcemia the dialysate calcium decreased to low calcium dialysate. Laboratory values should be controlled weekly until improvement is seen. One exception is hypercalcemia due to severe hyperparathyroidism and high-turnover bone disease. In addition, in patients with residual renal function, loop diuretics, i.e., furosemide may increase calcium excretion. If hypercalcemia is not corrected despite the discontinuation of active vitamin D metabolites, calcium-containing phosphate binders should be replaced by calcium-free phosphate binders to reduce the calcium load. Hypercalcemia is reported in up to 25% of patients taking calcium-containing phosphate binders ([1, 29], see recommendation 6).

**Recommendation 13**

The calcium phosphorus product should be kept within the normal range, at least below 5.0 mmol²/l² (60 mg²/dl²) (evidence). One of the risk factors for cardiovascular
morbidity was shown to be an elevated calcium-phosphorus product above 5.0 mmol²/l² (see also recommendation 2). If the calcium phosphorus product is elevated above this level, phosphate and/or calcium levels should be reduced. This may be achieved by an increase in phosphate binders, reduction/stopping of active vitamin D metabolites and use of low calcium (Ca++ 1.0–1.25 mmol/l) dialysate.

Recommendation 14

Parathyroidectomy has to be considered in case of severe, therapy-refractory hyperparathyroidism with radiological signs in combination with hypercalcemia and/or elevated calcium phosphorus product (evidence). Severe hyperparathyroidism may no longer react to even high doses of 1,25(OH)₂ vitamin D₃ and reduction of phosphate levels. The clinical observations in adults show that patients with at least one parathyroid gland larger than 0.5 cm³ or 1.0 cm in diameter usually do not respond to active vitamin D metabolites [81, 82]. Therefore, persisting grossly elevated PTH levels in the presence of high-dose active vitamin D metabolites, radiological signs of hyperparathyroidism on wrist X-ray and/or high serum calcium and normal phosphate and/or elevated calcium phosphorus product indicate the need for surgical parathyroidectomy. Medical parathyroidectomy by alcohol injection was described in adult patients [83], but to our knowledge not in pediatric patients. Parathyroid hormone stimulates bone turnover and regulates calcium homeostasis, both of which are of utmost importance in the growing skeleton. Therefore, subtotal parathyroidectomy or autotransplantation of parathyroid tissue is recommended in children or adolescents, avoiding hypoparathyroidism (84), review). However, these procedures carry the risk of recurrence of severe parathyroid tissue hyperplasia. The use of the new calcimimetic agents [85] may help to prevent the most severe hyperparathyroidism and therefore modify the approach to that condition.

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