Prevention of renal osteodystrophy in peritoneal dialysis

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Background. Renal osteodystrophy (ROD) is still one of the major long-term complications in end-stage renal disease leading to considerable morbidity. Despite some progress in understanding the pathogenesis of secondary hyperparathyroidism (sHPT) during recent years, prevention and treatment of ROD is still suboptimal, requiring surgical parathyroidectomy in 6 to 10% of all patients on dialysis after 10 years. In addition, the spectrum of bone lesions has changed, with non-aluminum-related adynamic bone disease (ABD) found in up to 43% of peritoneal dialysis (PD) patients.

Methods. Current recommendations concerning prevention of ROD in PD based on the literature and personal recent data were reviewed. The focus is on (i) the importance of early prophylactic intervention to prevent parathyroid gland hyperplasia, (ii) the pathogenesis of ABD, and (iii) the role of metabolic acidosis in ROD.

Results. There is ample evidence that sHPT starts early during the course of renal failure and results from both hypersecretion of PTH by parathyroid cells and glandular hyperplasia. As shown by experimental and clinical studies, established parathyroid cell hyperplasia is hardly reversible by pharmacological means, and therefore prevention of parathyroid cell proliferation needs to start early. Recent data from randomized trials document the efficacy and safety of low dose active vitamin D (0.125 to 0.25 μg/day) and/or an oral calcium substitute to prevent progression of sHPT in patients with mild to moderate renal failure. Since little is known about the pathogenesis, natural course and clinical impact of ABD in PD, specific therapeutic concepts have not yet been generated. Diabetes and advanced age are established risk factors, whereas the role of calcium and vitamin D overtreatment or the type of dialysis (PD vs. HD) are still controversial. Currently no evidence for different functional behavior of the parathyroids in ABD and sHPT has been found. The role of circulating or local factors such as cytokines, growth factors or the presence of advanced glycation end-product (AGE)-modified matrix proteins for the pathogenesis of either type of ROD deserves further investigation. Avoiding oversuppression of parathyroid glands and the use of low calcium dialysate may help prevent ABD. There is growing evidence that a correction of metabolic acidosis will influence ROD by both direct effects on the bone and on parathyroid cell function. New dialysate composition for CAPD with a high HCO₃ concentration will allow normalization of acid-base metabolism in PD patients. Their effects on ROD under long term conditions remain to be determined.

Key words: secondary hyperparathyroidism, adynamic bone disease, metabolic acidosis, peritoneal dialysis, vitamin D.

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Conclusion. Therapeutic efforts should aim to prevent the development of parathyroid gland hyperplasia and sHPT early during the course of renal failure, and should include the use of low dose vitamin D therapy and oral calcium substitution as well as correction of metabolic acidosis. Concerning ABD, more information is needed regarding the causes and consequences of this type of bone lesion to develop a more specific therapy.

Secondary hyperparathyroidism (sHPT) is still one of the major complications of chronic renal failure, and is associated with an increasing morbidity over time. The surgical parathyroidectomy rate is 38 per 1000 patient years after 10 years of dialysis [1]. Despite considerable progress in our understanding of the pathogenesis of renal osteodystrophy during the recent years [2], the therapeutic armamentarium is still insufficient or frequently not adequately used to prevent its development or progression [1, 3]. Major players in the pathogenic process are a decreased synthesis of biologically active vitamin D₃, hyperphosphatemia and the skeletal resistance to parathyroid hormone (PTH), all of which lead to or maintain hypocalcemia and hyperparathyroidism [2, 4]. Important cofactors like the deficiency of receptors for vitamin D, parathyroid hormone and calcium in parathyroid glands and bones, biologic resistance to active vitamin D and disturbances of the acid-base balance in uremia have now been identified to contribute substantially to the pathogenesis of sHPT and osteitis fibrosa [2]. The opposite end to osteitis fibrosa in the histological spectrum of renal osteodystrophy is represented by “adynamic bone disease” (ABD). Primarily found related to aluminum deposition in bones, ABD is now recognized with an increasing frequency as the predominant type of lesion in a considerable number of patients who were never exposed to aluminum, especially in the peritoneal dialysis population [5]. While there is still debate about whether ABD is actually a disease of the bone, the accompanying disturbances of calcium and phosphate metabolism undoubtedly predispose patients to serious extraossseous complications such as accelerated vascular, soft tissue and periarticular calcifications [6, 7].

The purpose of this review is to discuss strategies for the prevention of renal osteodystrophy and bone loss in chronic renal failure, with a special emphasis on peritoneal dialysis.
Due to space limitations I will concentrate on three topics: (1) the importance of early intervention to prevent parathyroid gland hyperplasia, (2) the “enigma” of non-aluminum related ABD, and (3) new aspects concerning the impact of metabolic acidosis and its correction on renal osteodystrophy in peritoneal dialysis.

PREVENTION OF PARATHYROID GLAND HYPERPLASIA

Disturbances of parathyroid hormone secretion by calcium are among the important factors leading to secondary hyperparathyroidism. As is evident from both experimental and clinical data, the increased secretion of parathyroid hormone results from an increased synthesis and secretion of PTH per cell as well as an increased number of PTH producing cells [2]. While both processes might be pathogenetically closely related, a number of recent studies elegantly confirmed what was suggested in early reports [8, 9]: the overwhelming importance of glandular hyperplasia for the disturbed response of the parathyroids to calcium in sHPT. Goodman et al studied the calcium regulated PTH release in 26 chronic peritoneal dialysis patients with different degrees of sHPT [10]. Performing dynamic tests of parathyroid function, they were unable to demonstrate a difference in the “set point” for calcium between patients with mild or severe sHPT. In addition, the sensitivity of the parathyroid glands to calcium was not different to that found in healthy controls. Comparable observations were reported by Indridason et al in hemodialysis patients with normocalcemic sHPT [11]. In contrast to patients with primary hyperparathyroidism or familial benign hypocalcemic hypercalcemia, which are disorders with a known defect of calcium sensing, parathyroid glands of patients with sHPT showed a normal calcium sensing. However, there was a significant correlation between the natural logarithm of parathyroid gland size (as assessed by ultrasonography), and the minimum PTH concentration under calcium infusion (% of baseline) and the slope of the calcium-PTH curve. The authors conclude that, at least in normocalcemic sHPT, calcium non-suppressible PTH secretion is determined by the size of the gland rather than by a defect of calcium sensing.

Although these reports strongly support the impact of glandular hyperplasia in the pathogenic process of sHPT, they do not necessarily exclude that differences in the set point for calcium might also be involved [2, 10, 11]. Indeed, in the study by Goodman et al the set point was highest in those two patients with the most severe sHPT who had to be parathyroidectomized [10]. Other authors described set point abnormalities especially in those hypercalcemic hyperparathyroid dialysis patients with the most advanced forms of sHPT (“tertiary” hyperparathyroidism), and with serum iPTH levels often exceeding 1000 pg/ml [12, 13]. It has been hypothesized that prolonged stimulation of parathyroid glands may trigger the transformation of parathyroid cells and result in a monoclonal, nodular type of glandular hyperplasia, as it is frequently found in the parathyroid tissue of these patients. In vitro studies confirmed that parathyroid cells from those areas have a reduced sensitivity to calcium [14].

From these studies it follows that besides suppression of PTH hypersecretion, therapeutic efforts aiming to prevent parathyroid gland hyperplasia are of particular importance. In experimental uremia in the rat, Szabo et al demonstrated that early intervention with 1,25-(OH)2 vitamin D3 prevents parathyroid hyperplasia, as measured by 3H-thymidine incorporation and glandular weight compared to solvent treated controls. In contrast, when treatment was delayed for 21 days a regression of established glandular hyperplasia was not achieved by 1,25-(OH)2 vitamin D3, despite a reduction in DNA-synthesis comparable to the early intervention group [15]. What is the situation in human beings? In a prospective trial of high dose oral versus intravenous calcitriol pulse treatment in chronic hemodialysis patients with advanced stages of sHPT, Quarles and coworkers failed to achieve sustained serum PTH reduction regardless of the mode of treatment in almost 40% of the patients. In addition, they were unable to document any regression of parathyroid gland size over a period of 36 weeks [16]. Similarly, Fukagawa et al found a correlation of the parathyroid gland size prior to calcitriol oral bolus therapy and the long-term success of this treatment in chronic dialysis patients. Only in patients with no or only minimally enlarged glands, as visualized by high resolution sonography, could a reduction in gland size and a long lasting suppression of plasma intact PTH (iPTH) be achieved. In those with already established glandular hyperplasia, especially with a glandular volume exceeding a threshold of 0.5 cm³, calcitriol treatment was unable to reduce gland size and control plasma iPTH over longer periods of time [17]. From experimental work it is still controversial whether calcitriol can induce apoptosis in parathyroid glands, the major pathway to induce reduction of parathyroid hypercellularity in vivo [18, 19]. As demonstrated recently in a well performed study by Ittel et al in parathyroid glands of patients after kidney transplantation, no apoptosis was demonstrable even after 24 months of intensive high-dose calcitriol bolus therapy. All patients had to be parathyroidectomized for recurrent hyperparathyroidism and hypercalcemia, showing extensive areas of the nodular type of hyperplasia [20].

A variety of factors has been identified to contribute to the progressive resistance of the parathyroid gland to calcium and vitamin D in secondary hyperparathyroidism. As has already been pointed out, with increasing gland size and prolonged stimulation of the parathyroids more and more areas of nodular hyperplasia are found within the glands. These nodules are characterized by a reduced expression of both the vitamin D and the calcium sensing receptor [21, 22]. Cells from these areas show an alteration
in the “set point” for calcium \emph{in vitro} [14]. In addition, monoclonal neoplastic growth has been observed in parathyroid glands from patients with sHPT in both areas of nodular and diffuse hyperplasia [23]. Refractoriness to vitamin D may further result from alteration of vitamin D binding to its specific receptor and of the hormone receptor complex to vitamin D receptor (VDR)-binding domains in the DNA [24]. Finally, there is now ample evidence from \emph{in vivo} and \emph{in vitro} studies that hyperphosphatemia stimulates PTH secretion independent from changes in calcium and calcitriol. However, whether phosphate directly promotes parathyroid cell growth is still a matter of debate [25].

These studies demonstrate that established parathyroid hyperplasia might not be reversed by currently available therapeutic means.

**IS THERE EVIDENCE THAT EARLY INTERVENTION IS ABLE TO PREVENT PARATHYROID CELL PROLIFERATION?**

Two more recent trials confirmed what has been suggested by early studies by Coen, Mazzaferrros and Bonucci [26], Nordal and Dahl [27], and Baker, Abrams and Roe [28]. Given the high incidence of sHPT and abnormal bone histology early in the course of renal insufficiency [29], both studies examined the effect of an early vitamin D treatment for prophylaxis of sHPT in patients with mild to moderate renal failure [creatinine clearance (CCr) 15 to 50 ml/min, serum creatinine (SCr) 1.4 to 6.5 mg/dl, respectively]. In the study by Hamdy et al, 76 patients were enrolled in a double-blind randomized prospective protocol [30]. Patients in the study group received 0.25 μg calcitriol/day over a period of 24 months compared to a control group receiving placebo. Biochemical, radiological and histological markers of renal osteodystrophy were assessed. After 24 months there was a significant improvement of bone histology with normalization of the histological findings in 42% of patients receiving calcitriol, whereas bone histology worsened in the majority of patients receiving placebo. Furthermore, the administration of calcitriol did not result in a more rapid decline of renal function, as hypercalcemic episodes were uncommon and adynamic lesions did not occur more often in the calcitriol treated group than in controls. Küster and coworkers used even lower doses of calcitriol (0.125 μg/day) in a randomized, placebo controlled trial in 45 patients with mild to moderate chronic renal failure [31]. This dose did not affect serum calcium or phosphate levels and did not induce hypercalcemia. Although bone histology was not available in this study, after one year of treatment calcitriol prevented an increase in intact PTH serum levels, while there was further worsening of sHPT in the placebo group. This effect was especially pronounced in patients with a serum creatinine at baseline of >3 mg/dl. In conclusion, both studies show evidence that early daily low dose therapy with active vitamin D is a safe and efficient therapy to prevent progression of sHPT with only little risk for worsening of renal function, hypercalcemia or hyperphosphatemia, and oversuppression of bone metabolism. It should be considered especially in patients whose iPTH levels cannot be controlled by correction of hypocalcemia and hyperphosphatemia by administration of calcium salts [32].

**ENIGMA OF NON-ALUMINUM INDUCED ADYNAMIC BONE DISEASE**

Adynamic bone disease (ABD) is histologically characterized by a low bone formation rate, a decreased number of both osteoblasts and osteoclasts and a delayed bone mineralization without increased osteoid formation or fibrosis [5]. The prevalence of this type of lesion has been increasingly described in ESRD patients over the last few years [33, 34]. Primarily related to aluminum deposition in bones, there is also a substantial number of patients presenting with this lesion who were never exposed to aluminum and have no or only limited detectable amounts of aluminum in bone histology [35]. According to Hercz et al [35] and Malluche and Monier-Faugere [33] peritoneal dialysis seems to predispose for ABD. In a recent cross sectional multicenter study in Europe, Coutenne et al found a prevalence of ABD of 43% in a peritoneal dialysis population with almost no exposure to aluminum containing phosphate binders [36]. ABD has also been described with a frequency of 12 to 48% in predialysis patients [29, 36–39]. There is still debate about the causes and natural course as well as the meaning of this “disorder” as an actual disease [5]. Long-term observations in patients with ABD showed both spontaneous conversion into osteitis fibrosa or persistence or even worsening of ABD after 12 to 24 months [37, 38, 40]. The reported increased frequency of severe vascular calcifications in ABD patients suggests that extrasosseous complications might influence the patient’s long-term prognosis even more than the skeletal lesions itself [40].

Beyond aluminum deposition several risk factors have been claimed to predispose for ABD: high calcium supplementation via calcium containing phosphate binders or high dialysate calcium concentrations, older age, diabetes and vitamin D therapy [5, 34–39]. Looking more carefully at a number of larger studies, only advanced age and diabetes turned out to be common risk factors, while vitamin D treatment and higher calcium substitution were associated with ABD only in a minority of studies (Table 1) [35, 36]. A common finding that might contribute to the decrease in bone metabolism in patients with ABD is the rather low plasma iPTH concentration [34–39]. Intact PTH levels below 150 pg/ml are highly sensitive and specific to detect ABD in chronic dialysis patients [41]. However, even in patients with ABD mean plasma iPTH levels are significantly higher than in a normal control population [34–39].
ABD histological or serological findings of renal bone disease. Serum IGFBP-2 and IGFBP-3 levels did not correlate with concentrations were not different between groups. In addition, both groups were clearly separated by iPTH serum levels, (CAPD) with biochemically and histologically defined ABD concentrations in 38 chronic dialysis patients (32 HD, 6 PD, suppl., suppliment; PD, peritoneal dialysis; iPTH, intact parathyroid hormone; ABD, adynamic bone disease; (+) positive correlation; (−) no correlation.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>Time on RRT/R</th>
<th>Diabetes</th>
<th>Calcium</th>
<th>Vitamin D</th>
<th>PD</th>
<th>iPTH</th>
<th>pmol/l</th>
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<td>68.0</td>
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Abbreviations are: RRT, renal replacement therapy; RI, renal insufficiency; PD, peritoneal dialysis, suppl., supplement; PD, peritoneal dialysis; iPTH, intact parathyroid hormone; ABD, adynamic bone disease; (+) positive correlation; (−) no correlation.

a Only predialysis patients tested
b Positive correlation between duration of renal insufficiency and risk of ABD

Thus, our data in a well characterized cohort of dialysis patients representing opposite ends of the spectrum of renal bone disease did not support a role for circulating IGFs in the pathogenesis of renal bone disease. However, these data do not exclude that alterations in the local, bone-derived IGF system might have a potential impact on the pathogenesis of this complication.

There is a growing body of evidence that advanced glycation end-products (AGE) are involved in uremic toxicity [48]. High serum concentrations of AGE have been found in ESRD patients compared to healthy controls [49, 50]. AGE modified molecules bind to various cells like monocytes or endothelial cells by binding to a specific receptor (RAGE). Binding of AGE to their receptor might stimulate synthesis and secretion of cytokines [tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1)] and growth factors [transforming growth factor-β (TGF-β), insulin-like growth factor-1 (IGF-1)] [48]. Targets of non-enzymatic glycation are especially molecules with a long half life, such as matrix proteins. Based on the observation that diabetics carry an increased risk for ABD, a lesion that might even be found in non-uremic diabetic patients [51, 52], we asked whether AGE modified bone matrix might participate in the development of ABD in end-stage renal disease (ESRD) patients. To date there is little information on the degree of AGE-modified proteins in bone matrix and the effects of glycated proteins on function of bone cells. Studying IL-6 excretion in human osteoblast-like cells (Saos) in response to non-enzymatically glycated albumin and collagen (type I), we observed no effect of AGE on IL-6 secretion into culture supernatants; slightly higher values were found in cells incubated on glycated type 1 collagen compared to non-glycated collagen treated controls. However, AGE-albumin and AGE-collagen significantly inhibited the dose dependent stimulation of IL-6 secretion in response to IL-1 in Saos cells (unpublished data; Fig. 1). While the cellular mechanisms of these effects are still the subject of further studies, our preliminary results suggest that the presence of AGE-modified matrix

### Table 1. Risk factors for the non-aluminum related adynamic type of renal bone disease

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<tr>
<th>Reference</th>
<th>Age</th>
<th>Time on RRT/R</th>
<th>Diabetes</th>
<th>Calcium</th>
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<td>68.0</td>
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</table>

Abbreviations are: RRT, renal replacement therapy; RI, renal insufficiency; PD, peritoneal dialysis, suppl., supplement; PD, peritoneal dialysis; iPTH, intact parathyroid hormone; ABD, adynamic bone disease; (+) positive correlation; (−) no correlation.

a Only peritoneal dialysis population tested
b Normal range 10–60 pg/ml

### Table 2. Biochemical markers of renal osteodystrophy and serum IGF-1 and IGF-2 levels in 38 chronic dialysis patients with non-aluminum related adynamic bone disease (ABD) and severe secondary hyperparathyroidism (sHPT)

<table>
<thead>
<tr>
<th></th>
<th>ABD (N = 25)</th>
<th>sHPT (N = 13)</th>
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<tr>
<td>Ca mmol/liter</td>
<td>2.3 ± 0.18</td>
<td>2.5 ± 0.24</td>
<td>NS</td>
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<tr>
<td>PO₄ mmol/liter</td>
<td>1.79 ± 0.38</td>
<td>2.24 ± 0.56</td>
<td>0.01</td>
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<td>iPTH pmol/liter</td>
<td>4.6 ± 2.8</td>
<td>78.6 ± 42.1</td>
<td>&lt;0.0001</td>
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<td>bAP ug/liter</td>
<td>6.5 ± 5.9</td>
<td>30.1 ± 23.3</td>
<td>0.003</td>
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<tr>
<td>Osteocalcin ug/liter</td>
<td>10.86 ± 5.29</td>
<td>34.66 ± 23.03</td>
<td>0.004</td>
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<td>IGF-1 ug/liter</td>
<td>211.8 ± 112.9</td>
<td>191.4 ± 53.3</td>
<td>NS</td>
</tr>
<tr>
<td>IGF-2 ug/liter</td>
<td>816.5 ± 217.5</td>
<td>799.8 ± 195.6</td>
<td>NS</td>
</tr>
<tr>
<td>Protein g/liter</td>
<td>68.0</td>
<td>69.2</td>
<td>NS</td>
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Data are given as mean ± sd. Statistical analyses were performed using the Mann-Whitney U-test.
proteins might alter the osteoblast’s response to regulatory hormones or cytokines. The amount and distribution of AGE-modified matrix proteins in patients with renal bone disease has not been reported yet and is currently being investigated.

Despite the increasing prevalence of non-aluminum related ABD in the dialysis population and especially in peritoneal dialysis patients, little is known about its pathogenesis. Clearly, more information is needed about the factors involved in the pathogenesis of this type of bone disease and its long-term impact as a “disease” before we can address therapeutic and prophylactic measures. Currently it is recommended that patients avoid therapeutic oversuppression of shPTH [5]. Vitamin D should not be given to patients with iPPTH < 2× the upper limit of normal. Lowering of dialysate calcium might be useful in this population to stimulate parathyroid activity and allow adequate substitution with calcium-containing phosphate binders. The development of new, non-calcium containing phosphate binding drugs [53] may provide a tool to ease the task of efficient phosphate control without the risk of hypercalcemia.

EFFECTS OF METABOLIC ACIDOSIS ON BONE MINERAL METABOLISM

There is ample evidence that bone mineral metabolism is altered by acute and chronic metabolic acidosis. For more detailed information on the mechanisms involved, the interested reader is referred to the recent in-depth review by Bushinsky [54]. Hydrogen ions are buffered by bone bicarbonate, exchanging sodium and potassium for protons. Decreases in pH directly release calcium from bone. In addition, chronic metabolic acidosis stimulates bone resorption mediated by increased osteoclast activity and inhibits osteoblast function, as demonstrated by decreased collagen synthesis in osteoblasts. Conflicting results exist concerning the effects of chronic metabolic acidosis on 1,25-(OH)_{2} vitamin D_{3} synthesis by 1-alpha hydroxylase activity [55, 56]. In uremia, metabolic acidosis has been associated with a higher frequency of osteomalacia, osteofibrosis and a diminished response to vitamin D therapy [57, 58].

DOES EVIDENCE EXIST THAT CORRECTION OF METABOLIC ACIDOSIS IMPROVES BONE MINERAL METABOLISM IN CHRONIC UREMIA?

In a welldesigned study by Lefebvre et al, 21 patients on hemodialysis were randomly allocated to treatment with either a conventional dialysate bicarbonate concentration (33 mmol/liter) or dialysis with an additional supplementation of bicarbonate to elevate predialysis serum-HCO_{3} to 24 mmol/liter for 18 months [59]. Progression of sHPT was documented by increased plasma PTH and bone histology in patients treated with the conventional solution, while there was no further progression of histological and serological findings in the patients with eubicarbonatemia. Furthermore, in patients with a suppressed bone formation rate at baseline, serum osteocalcin levels as a marker for increased osteoblast activity increased in the high bicarbonate group, but remained low in the control group treated with the conventional dialysate. Metabolic acidosis may further alter the sensitivity of the parathyroids to calcium, as pointed out recently by Graham and coworkers [60]. Performing dynamic studies of parathyroid function the authors could demonstrate that after optimal correction of metabolic acidosis in hemodialysis patients the PTH/ionized calcium curves were displaced downwards and to the left, indicating an increased sensitivity of the glands to calcium even within normal physiological limits.

In peritoneal dialysis hypobicarbonatemia and the degree of metabolic acidosis seem to be less pronounced and more stable than in hemodialysis. However, in most patients the average bicarbonate levels are lower than in the healthy population [61]. Conventional peritoneal dialysis solutions using lactate as buffer did not correct metabolic acidosis completely and resulted in a constant loss of bicarbonate into the dialysate [61]. With the development of new dialysate solutions containing high concentrations of HCO_{3} (39 mmol/liter), it seems now possible to completely normalize metabolic acidosis in chronic peritoneal dialysis patients [62]. Beyond normalization of acidemia, exchanging lactate for bicarbonate might provide a further potential benefit for parathyroid and bone cell function. As was shown in functional studies in red blood cells, the use of high lactate dialysate in peritoneal dialysis is not only toxic for cells within the peritoneal cavity, but may also affect cellular function systemically [63], a defect that was almost
completely abolished by the use of bicarbonate. Whether the use of new peritoneal dialysis solutions with high bicarbonate concentrations will show comparable effects in cells involved in bone and mineral metabolism, and whether normalization of metabolic acidosis will improve development and course of renal bone disease and prevent bone loss in long-term peritoneal dialysis remain subjects for future research. However, these new solutions might offer interesting new therapeutic options for treatment and prophylaxis of renal bone disease.

CONCLUSIONS

How can we translate what has been discussed throughout the previous chapters into practical guidelines for the prevention of renal bone disease in everyday clinical peritoneal dialysis practice?

1. Treatment of sHPT should be started early in the course of renal failure, that is, when C\(\text{Cr}\) falls below 50 ml/min. The first line of treatment should aim to control hypocalcemia and hyperphosphatemia by administration of calcium-containing oral phosphate binders. If intact PTH is not maintained within 2 to 3 times the upper normal limit by these measures, patients might benefit from a low dose vitamin D therapy (0.125 to 0.25 mg/day) to prevent further progression of glandular hyperplasia, particularly the development of nodular hyperplasia. Obviously, meticulous control of serum phosphate and calcium is mandatory, not only before but especially during vitamin D treatment.

2. Patients with advanced stages of sHPT may benefit from sonographic evaluation of the gland size to guide further treatment. Sustained control of sHPT by vitamin D is unlikely to be achieved if parathyroid volume exceeds 0.5 cm\(^3\), equivalent to a gland weight of about 1 g. If serum phosphate and calcium can be adequately controlled (PO\(_4\) < 1.8, Ca < 2.8 mmol/liter) high dose bolus vitamin D therapy is a valid therapeutic option independent of the route of administration (i.v. or orally) [16]. If iPTH does not respond after 6 to 8 weeks of vitamin D or serum phosphate or calcium cannot be controlled, then surgical parathyroidectomy will be the treatment of choice.

3. With regards to non-aluminum related ABD, information about pathogenesis and clinical impact is too scarce to allow specific therapeutic recommendations. However, the use of vitamin D is not indicated in these patients. Use of calcium containing phosphate binders might necessitate a reduction of dialysate calcium, since hypercalcemia is a frequent problem in ABD patients [64]. New calcium- and aluminum-free phosphate binding agents currently in development may become valuable alternatives in the treatment of patients with ABD [53].

4. Virtually no clinical study has assessed the effect of correction of chronic metabolic acidosis on renal bone disease in patients on peritoneal dialysis. However, as might be extrapolated from studies in HD patients, normalization of acidosis might improve the parathyroid response to calcium as well as act directly on osteoblast and osteoclast function. With the new bicarbonate-containing peritoneal dialysis solutions are opportunities to approach or achieve complete correction of metabolic acidosis without further loss of bicarbonate into the dialysate. In addition, the potential toxic effects of lactate on bone metabolism can be avoided. The clinical benefits of these solutions for the prevention of renal bone disease, especially on the long-term, must be assessed in future studies.

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