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Management of Secondary Hyperparathyroidism in Hemodialysis Patients

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1. Introduction

Secondary hyperparathyroidism (sHPT) represents the adaptive and very often finally maladaptive response of the organism to control the disturbed homeostasis of calcium, phosphorus and vitamin D metabolism caused by declining renal function. Dysregulation of calcium and phosphorus homeostasis leads to elevated levels of the phosphatonin fibroblast growth factor 23 (FGF23), decreased renal phosphorus excretion, increased serum phosphorus, and diminished synthesis of calcitriol (1,25(OH)₂D₃), the active form of vitamin D. These alterations result in increased secretion and synthesis of parathyroid hormone (PTH) and parathyroid cell hyperplasia (Cunningham et al., 2011).

Evidence is available that these disturbances in mineral metabolism lead to vascular (Goodman et al., 2000; Raggi et al., 2002) and valvular (Ribeiro et al., 1998) calcifications and are directly linked to an increased risk of cardiovascular morbidity and mortality as well as excess all-cause mortality (Covic et al., 2009). In accordance to a recent systematic review, the risk of cardiovascular and all-cause mortality is greatest with elevated serum phosphorus followed by increased serum calcium and PTH (Covic et al., 2009). Apart from extra-skeletal side effects, sHPT also leads to profound alterations in bone metabolism which become obvious in the different forms of renal osteodystrophy (Malluche & Faugere, 1990; Moe et al., 2006). This clinical syndrome encompassing mineral, bone and cardiovascular abnormalities has been termed CKD-related Mineral and Bone Disorder (CKD-MBD) (Moe et al., 2006). Furthermore, sHPT is thought to play a role in various other complications of end-stage renal disease as bone pain, bone fractures, muscle dysfunction, sexual dysfunction, disturbed hematopoiesis, immune dysfunction, pruritus and calcific uremic arteriolopathy (calciphylaxis) (Rodriguez & Lorenzo, 2009). An overview of the current understanding of the pathogenesis of sHPT is given in Figure 1.

In an attempt to improve clinical care, the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI™ [KDOQI]) has recommended target ranges for serum intact PTH, serum phosphorus and total corrected serum calcium (KDOQI, 2003). More recently, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines for diagnosis, evaluation, prevention and treatment of CKD-MBD have been published (KDIGO, 2009) and endorsed by the US KDOQI (Uhlig et al., 2010) and European Renal Best Practice (Goldsmith et al., 2010) groups. These latter guidelines have tried to provide evidence-based recommendations, but due to the very limited availability of high quality
**Fig. 1. Pathogenesis of secondary hyperparathyroidism.** Declining kidney function causes reduced renal conversion of 25(OH)D to 1,25(OH)_{2}D by CYP27B1 (25(OH)D-1α-hydroxylase) and elevated serum phosphorus levels due to diminished phosphorus excretion. Increased phosphorus concentration, decreased calcium concentration and markedly reduced serum calcitriol levels lead to increased PTH synthesis and secretion in the parathyroid glands. Elevated FGF23 expression, to counteract the reduced phosphorus excretion, downregulates residual renal 25(OH)D-1α-hydroxylase, additionally promoting the development of sHPT. These metabolic changes are accompanied by a variable downregulation and underexpression of the calcium-sensing receptor and vitamin D receptor on parathyroidal cells, rendering the parathyroid gland unable to respond appropriately to calcium and calcitriol. Dashed lines indicate counter-regulatory pathways. Abbreviations: FGF23, fibroblast growth factor 23; P, phosphorus; Ca^{2+}, calcium; CaSR, calcium-sensing receptor; VDR, vitamin D receptor; FGFR1, fibroblast growth factor receptor 1, PTG, parathyroid gland.

Clinical interventional trials with skeletal, cardiovascular or mortality end-points in this field, fewer and less mandatory recommendations are given compared to the older KDOQI guidelines. The achievement of these target ranges set by the KDOQI or KDIGO guidelines is quite challenging (Young et al., 2004) and failure to reach these targets has been shown to be associated with increased risk for death compared to simultaneously achieving the targets for all three biochemical parameters PTH, calcium and phosphorus (Danese et al., 2008).
The 84-amino-acid peptide hormone PTH has a very short half-life of two to four minutes after parathyroid secretion. It is metabolized to shorter fragments in the liver which are then excreted by the kidneys. With increasing renal failure and progressive CKD the proportion of these fragments with a 5 to 10 times longer half-life raises due to decreased renal clearance. Although the exact composition and possible function of the various PTH fragments are not yet fully elucidated, experimental data clearly found a clinically relevant biological activity of some of these fragments. Routinely used second-generation PTH assays, globally called “intact” PTH assays because they were thought to measure the full-length PTH 1-84 molecule only, recognize with various cross-reactivities (from approximately 50 to 100%) a PTH fragment, which co-elutes in high-performance liquid chromatography with a synthetic PTH 7-84 fragment. With progressive renal failure the amount of this and related PTH fragments gradually increases from about 20% in healthy individuals to about 50% in hemodialysis patients (Brossard et al., 2000). Therefore, at least in part, the progressive increase in measured PTH with decreasing renal function is also linked to the decreased renal metabolism and clearance of PTH 1-84 and its fragments. The different commercially available second-generation PTH assays have variable cross-reactivity with the PTH 7-84 fragment, therefore PTH measurements with different assays are not fully comparable and due to lacking standardization of PTH measurement sHPT patients might be classified differently according to KDOQI or KDIGO guidelines, resulting in different and due to misclassification potentially disadvantageous therapeutic interventions (Koller et al., 2004). Newer third-generation PTH assays, which show no cross-reactivity with the PTH 7-84 and related fragments, have been developed. Unfortunately, in all bone biopsy studies, which were later used to establish the KDOQI and KDIGO PTH target ranges, the first available second-generation PTH assay was used, but this assay is no longer commercially available. In an attempt to provide some kind of comparability of PTH measurements and consistent classification, correcting factors for the different second-generation PTH assays were proposed (Souberbielle et al., 2010).

Current therapeutic strategies include the modification of calcium and phosphorus balance through restricted dietary calcium and phosphorus intake and removal during hemodialysis, administration of phosphate binders, vitamin D receptor activators (calcitriol and newer vitamin D analogues) and the calcimimetic cinacalcet, and ultimately parathyroidectomy in very severe sHPT. These interventions have been shown to improve the biochemical parameters (PTH, calcium, phosphorus), bone histology or histomorphometry and cardiovascular calcification, but still there is lacking evidence that improvements in these surrogate parameters translate into better patient outcomes. Traditionally interventions to treat sHPT primarily aimed at bone health, but over the years new experimental insights into cardiovascular calcification and epidemiological data about associated cardiovascular morbidity and mortality risk switched the emphasis from bone to cardiovascular health.

2. Treatment of hyperphosphatemia

Declining renal function inevitably causes phosphorus retention due to decreased renal phosphorus clearance. This mechanism starts early in chronic kidney disease. However, hyperphosphatemia is prevented until the late stages of chronic kidney disease by an increase in FGF23 and PTH which control phosphorus homeostasis for a definite time. Initially, phosphorus retention stimulates FGF23 and PTH secretion, which in turn suppress
renal phosphorus reabsorption and increase renal phosphorus excretion. FGF23 also suppresses calcitriol \( (1,25(OH)\_2D\_3) \) production, which diminishes intestinal phosphorus absorption but allows increases in PTH levels. Whereas FGF23 suppresses PTH secretion in normal parathyroid glands, resistance to its effect occurs with further loss of kidney function because of decreased Klotho and FGF receptor 1 expression in the parathyroid glands and the kidney. Thus, as chronic kidney disease progresses to late stages, these homeostatic mechanisms are inevitably overwhelmed, hyperphosphatemia ensues, and the levels of PTH and FGF23 increase progressively (Cunningham et al., 2011).

Robust observational data show a clear association of higher serum phosphorus levels with cardiovascular events and mortality (Block et al., 1998, 2004). The exact threshold above which risk significantly increases is not definitely known and varies across the studies from 5.0 to 7.0 mg/dL (1.6 to 2.3 mmol/L) (Covic et al., 2009). However, it has never been determined in randomized placebo-controlled trials whether treating hyperphosphatemia to specific target ranges improves clinical patient outcomes. The KDIGO guidelines therefore suggest to decrease serum phosphorus levels toward the reference range in patients with chronic kidney disease 5D (KDIGO, 2009). Therapeutic interventions to treat hyperphosphatemia include restriction of dietary phosphorus intake, administration of phosphate binders and increasing the frequency or length of dialysis sessions.

2.1 Dietary phosphorus restriction
Dietary phosphorus assessment and restriction is the cornerstone of the treatment of hyperphosphatemia. Educational support and dietary guidelines should be offered to the patients by a skilled dietician. Restriction of dietary phosphorus intake, however, requires a reduction in oral protein intake, as protein-rich foods are the main source of dietary phosphorus (Shinaberger et al., 2008). Lowering protein intake can lead to malnutrition and protein-energy wasting and thereby increasing mortality in dialysis patients (Lacson et al., 2007). It is very important to avoid concomitant malnutrition by forced dietary protein restriction, as protein restriction as means to lower dietary phosphorus intake may outweigh the benefit of controlled phosphorus and may lead to greater mortality (Shinaberger et al., 2008). One possibility for overcoming the problem of concordant overall protein restriction and the risk of malnutrition with reduced dietary phosphorus intake would be to avoid phosphorus-rich ingredients that are added to processed foods and beverages (Sherman & Mehta, 2009a, 2009b). Contrary to natural sources of organic phosphorus, such as meat or dairy products, such phosphorus sources are dissociated from protein intake. Reducing the consumption of such phosphorus additives might help to decrease phosphorus intake without the risk of protein-energy wasting (Sullivan et al., 2009). Additionally, the intake of protein sources with low phosphorus to protein ratios might further help to limit phosphorus intake (Noori et al., 2010). Nutritional guidelines recommend a maximum of 800 to 1000 mg (25 to 35 mmol) daily dietary phosphorus intake (Fouque et al., 2007). Nevertheless, dietary modifications alone are generally not sufficient to reduce phosphorus intake sufficiently in most patients, but help to save phosphate binders and probably reduce the high pill burden.

2.2 Phosphate binders
The use of oral phosphate binders to block intestinal phosphorus absorption has been shown to effectively reduce serum phosphorus levels irrespective of the phosphate binder
class. Although no placebo-controlled randomized trial has been done so far to prove that reduction in serum phosphorus by the use of phosphate binders improves patient outcomes, a recent prospective observational study in a large number of incident dialysis patients has shown that the use of any phosphate binder (versus none) offers a clear survival benefit independent of absolute serum phosphorus concentration and co-medication (Isakova et al., 2009).

Available phosphate binders include the calcium salts calcium acetate and calcium carbonate, aluminium hydroxide, the polymeric anion-exchange resins sevelamer hydrochloride and sevelamer carbonate, lanthanum carbonate and the newer so far not well studied compounds ferric citrate, SBR759 (iron-based), magnesium/calcium carbonate and magnesium carbonate/calcium acetate. They differ in composition, phosphate-binding capacity, form and have specific potential advantages and disadvantages, which are summarized in Table 1.

Considering the different agents there are no data at present to favour one phosphate binder, because there is no proven superiority of any phosphate binder or binder class for relevant clinical outcomes. According to a recent systematic review and meta-analysis of available randomized controlled trials all phosphate binders decrease serum phosphorus levels compared with placebo. The newer drugs sevelamer hydrochloride and lanthanum carbonate do not result in superior control of biochemical parameters compared with calcium salts. In contrast, in head-to-head studies calcium salts enable a greater reduction of serum phosphorus than sevelamer hydrochloride. Whereas both calcium salts (calcium acetate and carbonate) do not differ with regard to serum calcium levels, sevelamer hydrochloride and lanthanum carbonate are associated with significantly lower rates of treatment-related hypercalcemia, which may result in decreased cardiovascular calcification. However, the finding of slower or less progression of cardiovascular calcification in sevelamer-treated patients is inconsistent across the studies. Studies revealed no difference in PTH suppression when comparing calcium acetate with calcium carbonate or lanthanum carbonate.

<table>
<thead>
<tr>
<th>Binder source</th>
<th>Form</th>
<th>Content (mineral/me- tal/element)</th>
<th>Phosphate-binding capacity</th>
<th>Daily dose</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium carbonate</td>
<td>tablet, capsule, chewable, gum, liquid</td>
<td>200 mg elemental Ca$^{2+}$ per 500 mg carbonate (40% elemental Ca$^{2+}$)</td>
<td>39 mg phosphate per 1 gramm calcium carbonate</td>
<td>1500 to 3500 mg (3-7 tablets)</td>
<td>effective phosphate-binding, inexpensive, readily available, long-term experience</td>
<td>potential for hypercalcemia and hypercalcemia-associated risks, gastrointestinal side effects</td>
</tr>
<tr>
<td>Calcium acetate</td>
<td>capsule, tablet</td>
<td>126.7 mg elemental Ca$^{2+}$ per 500 mg tablet, 169 mg elemental Ca$^{2+}$ per 667 mg capsule (25% elemental Ca$^{2+}$)</td>
<td>45 mg phosphate per 1 gramm calcium acetate</td>
<td>3000 to 6000 mg (6 to 12 tablets)</td>
<td>effective phosphate-binding, potentially higher binding capacity and lower Ca$^{2+}$ absorption than carbonate, inexpensive, long-term experience</td>
<td>potential for hypercalcemia and hypercalcemia-associated risks, gastrointestinal side effects, more costly than carbonate</td>
</tr>
<tr>
<td>Phosphate Binder</td>
<td>Form(s)</td>
<td>Dosage Options</td>
<td>Phosphate-Binding Capacity</td>
<td>Potential Complications</td>
<td></td>
<td></td>
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<td>----------------------------------</td>
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<td>-------------------------------------------------------------------------------</td>
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<td></td>
</tr>
<tr>
<td>Aluminium hydroxide</td>
<td>tablet, capsule, liquid</td>
<td>Varying with 100 to 600 mg aluminium per tablet 62.3 mg phosphate per 5 ml, 18.8 mg phosphate per 1000 mg</td>
<td>very effective phosphate-binding capacity</td>
<td>potential for aluminium toxicity, gastrointestinal side effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sevelamer-HCl</td>
<td>tablet, none 64 mg phosphate per 800 mg sevelamer-HCl</td>
<td>effective phosphate-binding capacity, no Ca²⁺ and metal content, reduces LDL-cholesterol, possible potential for reduced calcification same as sevelamer-HCl, but lower risk of metabolic acidosis</td>
<td>costs, potential for decrease in bicarbonate levels, in presence of hypocalcemia need for Ca²⁺ supplement, higher risk of gastrointestinal side effects compared to Ca²⁺ salts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sevelamer carbonate</td>
<td>tablet, powder none</td>
<td>same as sevelamer-HCl 2400 to 9600 mg (3 to 12 tablets)</td>
<td>same as sevelamer-HCl, assumed to have same disadvantages as sevelamer-HCl except decrease in bicarbonate levels, less well studied costs, gastrointestinal side effects, potential for accumulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lanthanum carbonate</td>
<td>chewable tablet, powder 250, 500, 750 or 1000 mg elemental lanthanum per tablet</td>
<td>NA 750 to 3750 mg (3 to 5 chewable tablets)</td>
<td>effective phosphate-binding capacity, no Ca²⁺, chewable, reduced pill burden effective, potential for lower Ca²⁺ load than pure Ca²⁺-based binders</td>
<td>potential for hypermagnesemia, gastrointestinal side effect, not well studied</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium carbonate/calcium acetate</td>
<td>tablet, 60 mg Mg per 235 mg MgCO₃, 110 mg elemental Ca²⁺ per 435 mg Ca²⁺ acetate</td>
<td>NA 705/1305 mg to 2820/5220 mg (3 to 12 tablets)</td>
<td>effective phosphate-binding capacity, potential for lower Ca²⁺ load than pure Ca²⁺-based binders</td>
<td>potential for hypermagnesemia, gastrointestinal side effect, not well studied</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferric citrate</td>
<td>capsule, 176 mg elemental iron per 1 g ferric citrate</td>
<td></td>
<td>potential for iron accumulation, not well studied, gastrointestinal side effects, less effective than Ca²⁺ salts</td>
<td>potential for iron accumulation, not well studied (1 phase I trial), gastrointestinal side effects, hypocalcemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBR759</td>
<td>powder, 1.25 g per sachet</td>
<td>powder form</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Table 1. Overview of available phosphate binders (adapted from KDOQI, 2003; KDIGO, 2009; Tonelli et al., 2010; Uhlig et al., 2010). Abbreviations: Ca²⁺, calcium; HCl, hydrochloride; Mg, magnesium; CO₃, carbonate; NA, not available.
carbonate with calcium carbonate, but found a significantly lower PTH reduction with sevelamer hydrochloride in comparison to calcium salts. When all studies were pooled, gastrointestinal side effects occurred more often with sevelamer hydrochloride than with calcium salts. With the use of sevelamer hydrochloride significantly lower serum bicarbonate is found, aggravating already existing metabolic acidosis. The new formula of sevelamer carbonate does not negatively influence acid-base status. A possible advantage of sevelamer is its significant reduction of LDL-cholesterol. However, no difference in all-cause mortality could be found comparing calcium acetate and carbonate, or sevelamer with calcium salts. All-cause mortality as endpoint has not been studied with all other phosphate binders (Navaneethan et al., 2009).

Hypercalcemia is a known side effect of calcium salts, especially when combined with vitamin D receptor activators. Persistent hypercalcemia necessitates a dose reduction or cessation of calcium salts as phosphate binders. The KDOQI guidelines suggest limiting the daily calcium intake from calcium-containing phosphate binders to 1500 mg per day for elemental calcium and 2000 mg per day for total intake of elemental calcium including the dietary calcium content (KDOQI, 2003). Nevertheless, there is no data available to recommend a specific upper limit of a safe amount of calcium intake. Restrictive use of calcium-based phosphate binders may be considered in the following situations (Cozzolino et al., 2011; Goldsmith et al., 2010):

- presence of cardiovascular disease
- presence of vascular or valvular calcification
- older age (>65 years)
- diabetes mellitus
- evidence of adynamic bone disease
- hypercalcemia

Although very effective, a prolonged (>3 months continuously, or >6 months cumulative) use of aluminium hydroxide should be avoided because of the potential toxicity of accumulated aluminium leading to encephalopathy, osteomalacia and anemia (Goldsmith et al., 2010).

Irrespective of the phosphate binder class the successful practical management of hyperphosphatemia with phosphate binders includes:

- concomitant dietary phosphorus restriction (especially phosphorus-rich additives)
- administration of phosphate binders with the meal
- individual dosing with respect to eating habits and serum phosphorus level

A new and promising concept for the management of hyperphosphatemia was recently developed to enable patients to self-adjust the phosphate binder dose in relation to the phosphorus content of each individual meal: “Phosphate Education Program” (PEP) (Ahlenstiel et al., 2010). Patients are taught to eye-estimate the meal phosphorus content based on “phosphate units” (PU; 1 PU is defined per 100 mg of phosphorus per serving size of the meal) and then phosphate binders are prescribed dependent on an individual phosphate binder/PU ratio. This concept is similar to the individualized adjustments of insulin dose to carbohydrate intake in the treatment of diabetes mellitus.

Novel agents under development for the treatment of hyperphosphatemia are MCI-196 (colestilan) (Locatelli et al., 2010), a non-metallic anion-exchange resin, and niacin and nicotinamid, which probably directly inhibit the sodium-dependent phosphate cotransporter Na-Pi-2b in the gastrointestinal tract (Muller et al., 2007).
2.3 Dialytic methods for phosphorus removal
Dialytic methods to improve phosphorus removal include prolonged (nocturnal) hemodialysis (Culleton et al. 2007; Walsh et al., 2010) and convective strategies (Tonelli et al., 2009).

3. Vitamin D therapy
3.1 Correction of vitamin D deficiency and insufficiency
Neither the normal nor the desirable target ranges for 25-hydroxyvitamin D (25(OH)D) levels are known in patients on hemodialysis. In accordance with patients without chronic kidney disease, 25(OH)D levels <12.5 ng/mL (<30 nmol/L) are defined as vitamin D deficiency, values <30 ng/mL (<75 nmol/L) as vitamin D insufficiency. Observational studies have shown an association between low 25(OH)D levels and adverse clinical outcomes (Holick, 2005; Wolf et al., 2007; Giovannucci, 2008). Although data from clinical trials are missing to show a survival benefit after increasing 25(OH)D levels in insufficient or deficient hemodialysis patients, current guidelines suggest to replete 25(OH)D stores in these patients on grounds of low costs, relative safety of repletion and potential therapeutic impact (KDIGO, 2009). After initial measurement and diagnosis of vitamin D deficiency, a supplementation using cholecalciferol or ergocalciferol may be initiated with remeasurement after 3 months of supplementation. There are no data regarding the choice of vitamin D product or the administration route. Altogether, oral repletion seems to be more favourable compared to intramuscular route in hemodialysis patients. In accordance with the general population a daily dose of 1000 to 2000 IU of cholecalciferol or a corresponding weekly dose are given (KDOQI, 2003; KDIGO, 2009; Uhlig et al., 2010). In a recent study in 107 hemodialysis patients, 91% of the patients had a serum 25(OH)D level higher than the target level of 75 nmol/L (30 ng/mL) after 3 months of monthly oral substitution of 100,000 IU (at first dialysis session of the month) (Jean et al., 2009). This approach seems to be safe and guarantee patient compliance. If hypercalcemia or hyperphosphatemia occurs, vitamin D repletion should be temporarily discontinued or abandoned. Table 2 gives an overview of the key differences between 25(OH)D and its “active” form 1,25(OH)₂D.

<table>
<thead>
<tr>
<th></th>
<th>25(OH)D</th>
<th>1,25(OH)₂D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total plasma concentration (recommended normal values)</td>
<td>30 to 50 ng/mL (75 to 125 nmol/L)</td>
<td>30 to 50 pg/mL (75 to 125 pmol/L)</td>
</tr>
<tr>
<td>Total plasma concentration (relative values)</td>
<td>1000</td>
<td>1</td>
</tr>
<tr>
<td>Binding affinity to vitamin D-binding protein (relative values)</td>
<td>1000</td>
<td>1</td>
</tr>
<tr>
<td>Free concentration (relative values)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Half-life</td>
<td>25 to 30 days</td>
<td>4 to 8 hours</td>
</tr>
<tr>
<td>VDR affinity (relative values)</td>
<td>1</td>
<td>500 to 1000</td>
</tr>
</tbody>
</table>

Table 2. Characteristics and differences of 25(OH)D and 1,25(OH)₂D. Abbrevations: VDR, vitamin D receptor.
3.2 Vitamin D receptor activators

Treatment of sHPT with active vitamin D receptor activators (VDRA) is a well-established therapeutic modality, and current practice guidelines recommend to treat patients with elevated and/or increasing PTH levels with a VDRA (KDIGO, 2009). Observational studies are indicating a survival benefit of VDRA in hemodialysis patients in comparison with patients without VDRA treatment (Teng et al., 2003, 2005; Tentori et al., 2006; Naves-Diaz et al., 2008). Again, prospective controlled randomised clinical trials indicating a benefit on patient-level clinical outcomes with VDRA therapy are missing but strongly awaited. Calcitriol, the physiological VDRA, is the natural regulator of parathyroid gland function and growth and exerts its effect on PTH secretion by inhibiting mRNA synthesis through its action on the vitamin D receptor (VDR), a highly specific receptor that acts as a transcription factor. In addition, calcitriol is able to inhibit PTH secretion by increasing calcium absorption in the intestine, while also increasing bone resorption and, consequently, calcium release from bone. Moreover, calcitriol regulates the expression of its own receptor, stimulating its synthesis. The deficit of calcitriol observed in hemodialysis patients as well as a transformation into nodular hyperplasia with progressive sHPT is associated with a decrease in VDR levels in the parathyroid gland. Decreased VDR expression may than cause resistance to VDRA. VDRA generally control sHPT well in patients with moderately increased hypertrophic glands and less well in patients with enlarged hyperplastic glands and should therefore be started early in the development of sHPT (Cunningham et al., 2011). Beyond the classical endocrine effects on parathyroid gland, bone and intestine, the pleiotropic paracrine and autocrine effects of vitamin D have been associated with improvement of cardiovascular risk factors, including increased renin activity, hypertension, inflammation, insulin resistance, diabetes, albuminuria and an improved immune response.

Besides the native active hormone calcitriol (1,25(OH)₂D₃), the two prodrugs alfacalcidol (1(OH)D₃) and doxercalciferol (1(OH)D₂) and the two vitamin D analogues paricalcitol (19-nor-1,25(OH)₂D₂) and maxacalcitol (22-oxa-1,25(OH)₃D₃) can be used. Paricalcitol and maxacalcitol (oxacalcitriol) bind directly to the VDR, whereas doxercalciferol and alfacalcidol need an enzymatic 25-hydroxylation activation step in the liver. So far no prospective, placebo-controlled and blinded clinical trial involving 22-oxacalcitriol, paricalcitol, or doxercalciferol has yet demonstrated additional clinical benefits when compared with calcitriol, nor have any studies been published showing that either calcitriol or alfacalcidol has an advantage over the other with respect to biochemical or clinical endpoints (Cunningham & Zehnder, 2011). Therefore, low dose therapy with calcitriol (e.g. 0.25 µg/d orally or 0.25 µg thrice weekly orally or intravenously as a starting dose) is recommended with elevated or increasing PTH levels (KDIGO, 2009). Characteristics and oral calcitriol equivalent doses of various available VDRA are presented in Table 3.

According to current practice guidelines, the target range for PTH is now 2-9 times the upper limit of the normal range (KDIGO, 2009; Uhlig et al., 2010; Goldsmith et al., 2010). This wide range takes into account a significant interassay variability of values obtained with different commercial PTH assays (Koller et al., 2004; Souberbielle et al., 2010), inability to uniformly predict bone histologic and histomorphometric states by means of PTH within this range and the epidemiological observation of increased all-cause mortality starting from PTH values >400 to 600 pg/mL (Uhlig et al., 2010). If there is no successful response with PTH reduction into the suggested target range, or dose-limiting side effects occur, especially hypercalcemia and hyperphosphatemia, a calcimimetic can be initiated instead or combined with a low dose of VDRA.

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VDRA Chemical structure Oral calcitriol equivalent dose (thrice weekly)

<table>
<thead>
<tr>
<th>VDRA</th>
<th>Chemical structure</th>
<th>Oral calcitriol equivalent dose (thrice weekly)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitriol</td>
<td>1,25(OH)\textsubscript{2}D\textsubscript{3}; natural hormone</td>
<td>oral 0.25 µg intravenous 0.5 µg</td>
</tr>
<tr>
<td>Alfacalcidol</td>
<td>1(OH)D\textsubscript{2}; synthetic prohormone</td>
<td>oral 0.5 µg intravenous 1 µg</td>
</tr>
<tr>
<td>Doxercalciferol</td>
<td>1(OH)D\textsubscript{2}; synthetic prohormone</td>
<td>oral 2.5 µg intravenous 5 µg</td>
</tr>
<tr>
<td>Paricalcitol</td>
<td>19nor-1,25(OH)\textsubscript{2}D\textsubscript{3}; synthetic analogue</td>
<td>oral 1 µg intravenous 2 µg</td>
</tr>
<tr>
<td>Maxacalcitol (Oxacalcitriol)</td>
<td>22oza-1,25(OH)\textsubscript{2}D\textsubscript{3}; synthetic analogue</td>
<td>NA</td>
</tr>
</tbody>
</table>

Table 3. Characteristics and oral calcitriol equivalent doses of vitamin D receptor activators (VDRA). Abbreviation: NA, not available.

4. Calcimimetics

Calcimimetics are allosteric modulators of the calcium sensing receptor that sensitize the receptor to extracellular calcium. This results in reduced PTH secretion and inhibited parathyroid cell proliferation (Nemeth et al., 1998; Chin et al., 2000). This decrease in serum PTH is accompanied by control of serum calcium and phosphorus levels in patients with sHPT as well as a halt or regression of parathyroid gland hyperplasia (Meola et al., 2009). Initial phase III trials and various observational studies have shown that cinacalcet enables more patients to reach the recommended biochemical targets (Block et al., 2004; Lindberg et al., 2005; Urena et al., 2009) and allows sustained biochemical control for long term up to 3 years (Sprague et al., 2009). At present cinacalcet hydrochloride is the only calcimimetic available for clinical use. In contrast to VDRA, cinacalcet decreases all three important biochemical parameters of CKD-MBD (PTH, phosphorus, calcium) (Urena et al., 2009). In addition to excellent results on laboratory parameters, cinacalcet has also shown favourable effects on cardiovascular hospitalization, bone fracture rate, parathyroidectomy rate and quality of life (Cunningham et al., 2005). In a prospectively designed observational study use of cinacalcet on top of standard sHPT therapy with VDRA and phosphate binders resulted in a 26% lower all-cause mortality and a 24% lower cardiovascular mortality than in patients without cinacalcet, with the largest survival benefit for patients with most severe sHPT (PTH >600 pg/mL) (Block et al., 2010). The ongoing double-blind, randomised placebo-controlled EVOLVE trial (Evaluation of cinacalcet HCl therapy to lower cardiovascular events) currently determines whether cinacalcet reduces all-cause mortality or non-fatal cardiovascular events (Chertow et al., 2007).

Generally, initial therapy starts with a daily dose of 30 mg followed by dose-titration every 2 to 4 weeks if necessary. Serum calcium levels must be monitored regularly because of its known hypocalcemic effect.

Whereas VDRA reduce PTH gene transcription and hormone synthesis over a period of several hours or even days, cinacalcet inhibits PTH secretion within minutes, with a maximal decrease occurring within 2 to 4 hours after administration. Besides gastrointestinal side effects, hypocalcemia is one of the most common adverse events seen with cinacalcet. It is thought to occur after decreased mobilization of calcium from bone.
caused by lowered PTH levels. In most patients, this hypocalcemia can be successfully managed with dose adjustments or a combination with low doses of VDRA in patients with moderate to severe sHPT. Clinical trials have demonstrated the superior suppression of PTH production and control of calcium and phosphorus in hemodialysis patients who use cinacalcet, both as adjunctive therapy to VDRA and as primary therapy with reduced doses of VDRA, compared with sHPT therapy with VDRA and phosphate binders only (Chertow et al., 2006; Block et al., 2008; Fishbane et al., 2008; Messa et al., 2008).

5. Parathyroidectomy
Persistently increased serum PTH levels >800 pg/mL (88.0 pmol/L) in presence of hypercalcemia or hyperphosphatemia refractory to medical therapy and calcific uremic arteriolopathy (calciphylaxis) with concomitantly elevated PTH levels are an indication for surgery (KDOQI, 2003; KDIGO, 2009). Subtotal and total parathyroidectomy (PTX) with or without forearm autograft arose as a treatment option in the 1990s (Tominaga et al., 1997) and PTX continues to be a primary therapeutic option for refractory sHPT in both Europe and the US. Rates of PTX increased for US patients on hemodialysis from 1998 to 2002 despite an increase in therapeutic options (Foley et al., 2005). The frequency of PTX across Europe has remained relatively stable since the mid-1980s (Malberti et al., 2001) and is lower in older patients (Pelletier et al., 2010).

PTX effectively decreases PTH, calcium and phosphorus and offers the highest percentage cure for sHPT, compared to all other medical and surgical treatments. However, recurrent hyperparathyroidism can be observed in 10 - 70% of patients dependent on follow-up time (Johnson et al., 1988; Gagne et al., 1992; Gasparri et al., 2001). For total parathyroidectomy with autotransplantation an intra-operative selection of parathyroid tissue with diffuse hyperplasia but low proliferative potential (and exclusion of nodular tissue) is feasible and minimizes the risk of graft-dependent recurrent hyperparathyroidism (Neyer et al., 2002). Alternatively to surgery, ultrasound-guided percutaneous fine-needle ethanol injection into nodular hyperplastic parathyroid glands is very common in Japan (Giangrande et al., 1992; Kitaoka et al., 1994; Fukagawa et al., 1999). Apart from ethanol, also calcitriol or novel VDRA can be directly placed into enlarged parathyroid glands using the same technique (Shiizaki et al., 2003).

To date no specific guidelines considering sHPT treatment in hemodialysis patients on kidney transplant waiting list have been established. After successful kidney transplantation persistent HPT can be observed in up to 25% of patients one year after transplantation despite adequate renal graft function. Severity of sHPT at time of transplantation was found to be a significant indicator of persistent HPT (Evenepoel et al., 2004). If indicated, therapy for persistent HPT should be initiated about three months after renal transplantation because further spontaneous improvement thereafter is rare. Because this special situation of persistent HPT after transplantation is usually accompanied by hypercalcemia and hypophosphatemia, conventional therapy with phosphate binders, VDRA or calcium supplements is not indicated in most patients. Therefore, PTX is the preferred treatment option in this situation and has been shown to be effective, safe, though associated with a mild deterioration of graft function in the early postoperative phase but similar graft survival in the long-term compared to kidney transplant patients without PTX and linked to a blood pressure and lipid lowering effect (Triponez et al., 2008). Recently, also cinacalcet has been proposed to offer an alternative therapeutic option to PTX, although not approved.
for the use in this situation and cost-intensive if used for many years (Kruse et al., 2005; Serra et al., 2005; Srinivas et al., 2006; Zitt et al., 2007). Therefore, we believe that a good and early control of sHPT prior to kidney transplantation is mandatory. This should be initially done using all medical options including cinacalcet, but if unsuccessful in control of severe sHPT proceeding straight to PTX for an optimal and cost-effective treatment. Randomized clinical trials directly comparing medical with surgical therapy of sHPT are lacking.

To avoid severe postoperative hypocalcemia ("hungry bone syndrome), pre-/peri- and postoperative calcium and calcitriol supplementation (e.g. 1 to 2 g elemental calcium thrice a day, 1 to 4 µg calcitriol per day; parenteral calcium substitution if symptomatic hypocalcemia is present with 1 to 2 mg elemental calcium/kg/h) must be guaranteed along with frequent controls of serum calcium levels. In case of recurrent or persistent hyperparathyroidism after parathyroidectomy, cinacalcet has been shown to be a viable and safe treatment option (Zitt et al., 2010).

6. Dialysate calcium concentration

A near-neutral calcium flux could be expected in patients with a dialysate calcium concentration of 1.25 mmol/L (2.5 mEq/L), although there is considerable interindividual variability among patients (Hou et al., 1991; Argiles et al., 1993). Based on calcium kinetic modelling even lower dialysate calcium concentrations of 1.0 mmol/L (2.0 mEq/L) might be needed to avoid net positive calcium balance (Gotch et al., 2010). The risks of hemodynamic instability and cardiac rhythm disturbances with a very low dialysate calcium concentration must be kept in mind (Drueke & Touam, 2009). Overall calcium balance is influenced by dietary calcium intake, vitamin D level, calcium-containing phosphate binders, use of VDRA and calcimimetics and dialysate calcium concentration. Therefore, selecting an individual dialysate calcium concentration is based on various parameters and must always be a compromise between the need to guarantee cardiovascular stability during the hemodialysis session and the goal to maintain normal bone turnover and mineralization in order to avoid bone pain and fractures but avoid extraskeletal calcification.

7. Summary

Whereas there are insufficient high-quality randomized controlled trials in the field, this shortcoming should not lead to a nihilistic approach to the relevant clinical problems of hemodialysis patients with sHPT. Nevertheless, because of insufficient clinical data, a single treatment modality, be it phosphorus binders, vitamin D substitution with inactive forms or vitamin D receptor activators, calcimimetics or parathyroidectomy may not claim to be uniformly superior to the others, and a wider therapeutic window often prompts the use of a combination of these options and individualization of sHPT management. The ultimate goal is to improve the very poor survival of hemodialysis patients, so any suggested approach for the management of sHPT should be tested.

8. References


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Hemodialysis (HD) represents the first successful long-term substitutive therapy with an artificial organ for severe failure of a vital organ. Because HD was started many decades ago, a book on HD may not appear to be up-to-date. Indeed, HD covers many basic and clinical aspects and this book reflects the rapid expansion of new and controversial aspects either in the biotechnological or in the clinical field. This book revises new technologies and therapeutic options to improve dialysis treatment of uremic patients. This book consists of three parts: modeling, methods and technique, prognosis and complications.

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