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The Importance of Adherence in the Treatment of Secondary Hyperparathyroidism

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Abstract
Secondary hyperparathyroidism (SHPT) is a frequent condition in the presence of chronic kidney disease (CKD). In CKD patients, SHPT is reported to increase both morbidity and mortality, especially cardiovascular. The difficulty in the treatment of SHPT in clinical practice is frequently encountered from a not always adequate conduct of the clinicians and a common non-compliance to the therapy of CKD patients. In this review, the greatest difficulties from clinicians and CKD-patients' point of view in the treatment of SHPT will be addressed, with particular attention to those related to dialysis features, nutritional habits, and medical therapy.

Introduction

Secondary hyperparathyroidism (SHPT) is a frequent condition during chronic kidney disease (CKD). It results from the many disarrangements of mineral metabolism (MM) that are typical of CKD. These include fibroblast growth factor-23 increase, vitamin D reduction and in the late stages of the disease, calcium (Ca) and phosphorus (P) modifications. SHPT is strongly related to both cardiovascular and bone diseases and contributes to the definition of chronic kidney disease-mineral bone disorder (CKD-MBD) [1]. Despite the importance of a good control of SHPT, in recent years, DOPPS data have described both in the United States and Europe the progressive increase of the mean levels of parathormone (PTH) levels in the dialyzed population. Also some recent Italian data have confirmed a not optimal control of MM parameters in the CKD population, in part related to therapeutic non-compliance [2].

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The majority of difficulties in the treatment of SHPT results from both medical and CKD patients related factors. The absence of guidelines able to indicate with a high grade of evidence a specific target for PTH, represents a main problem [3]. In addition, it is important to underscore that the presence of different guidelines and consequent targets in different continents might create confusion and increase the lack of medical adherence in the treatment of CKD-MBD. Considering the low grade of evidence and the commercialization of many assays for the dosage of PTH [4], the recently reviewed CKD-MBD KDIGO guidelines confirm maintaining PTH levels in the range of approximately 2–9 times the upper normal limit for the assay used [5]. This could also explain why in recent years a worse awareness of the target levels has been reported among dialysis centers worldwide [6].

Clinicians can operate in different areas in SHPT therapy. Unfortunately, it is not unusual to be in the presence of hostile, frequently depressed, and anxious patients that make the correct actuation of the treatment complicated and difficult [7].

In this review, three different areas of treatment: (1) prescription of an efficient dialysis; (2) nutrition; (3) drug therapy will be discussed.

The Problem of Adherence in SHPT Treatment: Which Dialysis for Which Patient?

An efficient dialytic schedule is extremely important for obtaining a good control of SHPT [8].

Of note, the main target of dialytic treatment for SHPT is the correction of Ca and P disarrangements and consequently of PTH.

From the beginning of the treatment, a "personalization" of the therapy is advisable. Unfortunately, due to different points of view and problems of communication between caregivers and patients, the reach and optimization of therapy are often difficult.

Dialysis Schedule

Duration and frequency of dialysis are essential for obtaining a good P removal. In hemodialysis (HD) patients, P removal is highly influenced by pre-dialytic session levels and by dialytic clearance of P [9, 10].

In the study published by Eloot et al. [11], 9 stable chronic HD patients were dialyzed for 4, 6, or 8h. The results of this study indicated the significant proportion of total P removal, according to the duration of the treatment. Interestingly, the maximum reduction rate of P was obtained during the first 120 min in all the different duration schedules, reflecting the importance of P rebound following P stabilization during the course of dialysis.

Also, the frequency of dialysis seems to have an impact on P removal. In 2005, 77 HD patients had been followed for 12 months. Twenty-six of them were assigned to a short daily hemodialysis schedule (SDHD: 6 sessions/week of 3 h each one), whereas 51 to chronic hemodialysis schedule (CHD: 3 sessions/week of 4 h each one). During the 12 months of follow-up, a significant reduction of P and PTH was observed only in SDHD. Of note, the reduction of PTH in that group was also obtained using a higher dose of active vitamin-D, probably thanks to its better dialysis efficiency. In addition, a significant reduction of left ventricular mass index only in SHD patients was reported, with a significant correlation between the percent changes of P and left ventricular mass index, evaluated both at baseline and after 1 year of follow up. SDHD and percentage decrease in P resulted in the best independent predictors of LMVI reduction. The effect of dialysis frequency was demonstrated also in moderate-severe vascular calcifications of feet and hands, which were significantly lower in the SDHD [12]. In a more recent trial, MM parameters and the need of P binders were significantly improved with a daily home nocturnal dialysis schedule (DNHD: target session time > 6 h). Compared to both in center conventional HD (CHD: target session time < 4 h), DNHD had a mean reduction of 1.24 mg/dL in P. In addition, 73% DNHD patients did not require P binders at month 12 compared to only 8% of patients assigned to CHD [13].

The choice of the dialysis technique is another hard point in the SHPT therapy. Some studies have evidenced a higher P removal capacity for the post-dilutional hemodiafiltration (post-HDF) compared to the conventional HD. In 22 patients, in 2006 a comparison between high flux-HD and post-HDF, demonstrated a +19% P removal in post-HDF [14]. More recently, the higher P removal in HDF was also confirmed in Italian studies with a bigger number of patients [15, 16]. In 493 HD patients, the CONTRAST study compared 242 patients who were shifted from low-flux-HD to HDF to 251 patients who remained on low-flux HD. Significant lower P levels and a higher proportion of patients reaching P treatment targets (5.5 mg/dL) in the HDF group were found. Moreover, in HDF the use of P binders was significantly lower than in the low-flux HD group [17].

Also, peritoneal dialysis (PD) leads to a good P removal. Continuous Ambulatory Peritoneal Dialysis seems to be slightly more effective than Automated Peritoneal Dialysis at peritoneal phosphate clearance, especially in low transporters patients [18].

Calcium Balance and Ideal Dialysate Calcium

Global Ca balance (CaB) in CKD patients can be defined as the difference between the total intake and losses of Ca.

Ca intake is influenced principally by intestinal absorption and therapeutic Ca (i.e., vitamin D, calcium-containing phosphate binders and calcium supplementation), whereas Ca losses result from fecal and urinary excretion. In dialysis patients, an important parameter to take into account in the evaluation of global CaB is the dialysate calcium (DCa). It is important to underscore that the continuous changes in therapeutic practice, and the lack of consistent studies in this field, are responsible for the absence of consensus on what should be the ideal DCa in HD patients. Certainly, DCa has an impact on global CaB and MM parameters. A study comparing the three different DCa concentrations have demonstrated that, compared to DCa > 1.25 and < 1.25 mmoL/L that expose patients to positive and negative CaB, respectively, DCa = 1.25 mmol/L is associated to a neutral one. Beyond Ca levels, DCa variations might influence the other MM parameters also significantly, especially PTH [19].

In 2016, the effect of lowering of DCa on the progression of coronary calcifications (CAC) and on bone turnover was investigated. The 425 HD patients studied were randomized in two groups and followed up for 2 years. In the first group, 212 patients treated with low DCa (1.25 mmol/L) were included (L-DCa). The remaining 213 patients were assigned to the high DCa (1.75 mmol/L) group (H-DCa). No difference in baseline biochemical characteristics and CAC was present. Interestingly, biochemical evaluation at 2 years demonstrated lower Ca and higher P, PTH, and alkaline phosphatase levels in the L-DCa group than in the H-DCa group. During the follow-up, an increase in CAC was found in both groups. The progression rate of CAC was, however, significantly less in L-DCa than in H-DCa. In addition, the prevalence of histologically diagnosed low bone turnover decreased from 85.0 to 41.8% in the L-DCa. No changes in H-DCa were found. At the end of follow-up, L-DCa group showed higher bone formation rate, trabecular thickness, and bone volume than H-DCa [20].

An influence on MM parameters mediated by different Ca concentrations in peritoneal solutions has also been described. In 2004, Sanchez et al. [21] reported higher PTH levels and oral intake of Ca salts in PD patients treated with low Ca PD solutions (1.25 mmol/L) compared to those treated with 1.50 mmol/L Ca PD solutions. In this context, the evaluation of MM parameters, and in particular of PTH, could be used as an indirect indicator of CaB changes.

In the recently published KDIGO 2017 guidelines, DCa between 1.25 and 1.50 mmol/L is suggested both in HD and in PD.

Briefly, DCa individualization might be considered as an additional therapy in a more global strategy together with P binders, vitamin D, and calcimimetics.

The Problem of Adherence in CKD-MBD Treatment: Nutrition

Nutrition really impacts the control of SHTP. Unfortunately, the correction of nutrition is not always considered before drug therapy, and patients are not adequately informed about food contents. In addition, public health services do not generally consider nutrition counselling to be of great importance. Recent data have demonstrated that in the USA, only 12% of office visits include counselling about diet in patients affected by cardiovascular disease, diabetes, obesity, hypertension, and cancers [22]. Nutrition counselling in CKD patients might aid in obtaining not only a better control of MM parameters, and in particular of P, but also of other metabolic anomalies typical of uremic status.

The regulation of P intake strongly influences the levels of serum P. A P-restricted diet should start from the identification, and food with many phosphorus additives, for example, prepared frozen food, dry food mixes or packaged meat should be avoided [23]. Additives are used for many reasons, such as improved color or extended shelf life [24]. Moreover, attention to cooking habits should be stressed: boiling food may remove, in addition to sodium and potassium, also a considerable quantity of P. The use of simple and simply understandable ingredient information on food packaging, could support the caregivers in this important goal [25].

Recently, strategies to increase the dietary adherence to nutritional advice have been provided. Among them, the "talking control" principles and the integration with patient-owned technology (for example, apps), are the most used [26].

The Problem of Adherence in CKD-MBD Treatment: the Drug Therapy

Drug therapy is the third level in the treatment of SHPT. Theoretically, drug therapy should be considered after a global optimization of both dialysis and nutritional habits. Unfortunately, the frequent lack of availability

Table 1. Principal phosphate binders and their characteristics

Binder	Mineral content	Accumulations	Pill burden	Cost	Advantages	Disadvantages
Calcium carbonate	400 mg of Ca element per g	Calcium +++	High	Low	Effective, readily available	Risk of hypercalcemia, calcium overload, PTH suppression, ABD, extrascheletral calcifications
Calcium acetate	250 mg of Ca element per g	Calcium ++	High	Low	Effective, readily available	Risk of hypercalcemia, calcium overload, PTH suppression, ABD, extrascheletral calcifications
Calcium acetate/ Magnesium carbonate	110 mg of elementar Ca and 60 mg of elementar Mg per tablet	Calcium + Magnesium +	High	Low	Effective, less risk of Ca overload compared to pure calcium-based binders	Risk of hypermagnesaemia
Aluminium hydroxide	From 100 to >200 mg/tablet	Aluminium ++	Low	Low	Effective	Bone, hematological and neurological toxicity
Sevelamer	None	–	High	High	Effective, better lipid profile, benefit on vascular calcifications	Price
Lanthanum	500, 750, and 1000 mg of elementar lanthanium per tablet	Lanthanum +	Low	High	Effective	Price, accumulation in bone, long-term clinical consequences unknown
Sucroferric Oxyhydroxide	500 mg of iron per tablet	Fe -	Low	High	High P binding capacity at gastrointestinal pH	Gastrointestinal tolerance

ABD, adynamic bone disease.

of organizational and logistic resources needed for optimizing dialysis treatment and poor compliance of patients to nutritional prescriptions, often make drug therapy a necessary approach in most dialyzed patients. The use of many drugs permits the individualization of therapy. One of the main problems is the strong pill burden.

Phosphate Binders

Phosphate binders (PB) are probably the most used drugs in dialysis patients. Their effect on intestinal P absorption is useful in the treatment of hyperphosphatemia. Nowadays the absence of clear guidelines and of randomized interventional studies able to indicate with high evidence the first line PB to use, makes PB therapy probably one of the most personalized therapies for CKD patients.

Also, many PB are available, and their characteristics are summarized in Table 1. Generally, PB are classified into two main classes: calcium-containing PB and calcium-free PB. Despite the high number of PB present, in Europe only 52% of HD patients are reported to maintain the serum phosphate levels within KDOQI targets [27]. This can be explained in part to a reduced compliance to these drugs due to the frequent side effects, especially gastrointestinal, that these drugs cause and by the frequently high number of pills needed in the treatment.

The following points are important in the choice of PB.

First is the composition. The presence of some minerals, such as Ca, aluminum or lanthanum, could expose patients to some general clinical effects, caused by their accumulation. For example, a prolonged use of aluminum-containing-PB, as used in the past, had been associated to cerebral, hematologic, and bone toxicity [28]. Similarly, a bone toxicity has also been described for lanthanum [29]. Ca-containing PB are characterized by an optimal cost/effect ratio. But these drugs, if used without control, can induce high Ca-element exposition of patients, facilitate the development and/or progression of extra-osseous calcifications, and bone dynamicity [30].

The use of Mg supplements or of Ca-Mg containing PB could reduce Ca exposition and simultaneously correct Mg levels, frequently low in CKD patients, through exposing to a Mg overload. Moreover, a reduction of P and PTH, and a modulation of vascular calcification and bone mineralization processes could be obtained [31]. Recently, iron-based PB have been released. Sucroferric oxyhydroxide and iron citrate are the most used. Both drugs, not inferior to the other PB, have a good intestinal phosphate binding capacity, obtained with a reduction in the average amount of daily pills. The major problem that complicates the compliance to this group of PB is gastrointestinal discomfort. In any case, iron-based PB might represent a good option in the treatment of hyperphosphatemia [32–33].

Second point to take into account in PB prescription is the pill burden, since P control is frequently not possible only with one class of PB. Furthermore, a combination of different molecules is often required to reduce the accumulation effect of using high doses of a single PB. In addition, most of the calcium-free PB are burdened by a higher cost. A recent study, performed in 233 dialysis patients, has estimated the overall pill burden of 19 ± 12 pills/day. Interestingly, in this cohort, PB were responsible for more than 50% of the total daily pill burden. A sub-analysis performed on the same cohort has demonstrated a progressive reduction of the global adherence and of the quality of life with an increase of pill burden [34].

Vitamin D Therapy

Vitamin D deficiency in CKD patients is a two-faced problems, since, in addition to the high prevalence of reduced availability of the native form, which is also highly represented in the general population, a reduced synthesis of the most active vitamin D metabolite (calcitriol) is often evident in the late stages of CKD, due to the reduced renal mass and increased fibroblast growth factor-23 levels [35].

In addition to the well-known role of Vitamin D in MM, a role of its deficiency in the increased cardiovascular morbidity and mortality and in the acceleration of renal function loss has been suggested [36].

Also, Vitamin D supplementation is complicated by many problems related to the adherence to the therapy. As for other drugs, the problem of adherence in vitamin D supplementation is more pronounced in younger patients [37]. The possible reasons of this phenomenon might be: first, an insufficient understanding by the patient on the importance of the regular adherence to therapy, associated vitamin D supplementation to a "general vitamin supplementation"; second: the unusual and less controlled formulations, especially for native vitamin D, in drops or vial is associated with frequent omissions. The possibility of using intravenous formulations of active vitamin D that can be injected at the end of HD, has drastically reduced the problem of adherence for the supplementation of the active form of vitamin D in HD patients, with certainly a better control in SHPT. Nevertheless, the scarce evidence reported in the literature of the long-term benefits provided from active Vitamin D supplementation and the lack of clear guidelines in this regard, leads to a high degree of medical non-adherence [38, 39].

Differently to active vitamin D, it is debated if native vitamin D supplementation could alone be able to control SHPT in CKD patients. Recently, a novel formulation of native vitamin D, the extended-release (ER) calcifediol has been tested with this aim in 429 patients (CKD stage 3 or 4), randomized 2:1 to receive daily pills containing oral ER calcifediol (30 or 60 μg) or placebo once daily for 26 weeks. In a subsequent open label extension study in which calcifediol was administered without interruption for another 26 weeks, 298 patients were entered. The results are really interesting. In fact, in the cohort studied, oral ER calcifediol was found to be safe and effective in treating SHPT and correcting the underlying vitamin D insufficiency [40].

In the future, this formulation might help to obtain a better control of SHPT in CKD patients.

Calcimimetics

Calcimimetics have provided a new important alternative for the treatment of SHPT. Nowadays in this class of agents, two molecules are commercialized: cinacalcet, an oral allosterically binder of the calcium-sensing receptor (CaSR) and the newly released etelcalcetide, an intravenous direct antagonist of the CaSR. Both molecules increase the response of CaSR to serum calcium.

DOPPS data have reported a progressive reduction of parathyroidectomy incidence since calcimimetics have been released [7].

The first study in which the treatment with cinacalcet and the unrestricted conventional care have been compared is the OPTIMA study. In this multicentric trial, 184 HD patients with poorly controlled SHPT (PTH = 507 ± 143 pg/mL), had been treated with conventional care and compared with another 368 patients (PTH = 505 ± 147 pg/mL) with the same clinical characteristics treated with cinacalcet-based regiment. After a 16-week dose optimization, a 7 week of efficacy assessment phase had been

Table 2. General suggestions to improve adherence

Dialysis	Use of intravenous drugs during HD Talk with patients about the importance of dialysis optimization Carefully evaluate dialysis settings Nursing support
Nutrition	Talk with patients about alimentation Use alimentary diary Nutritionist support Iconography Nursing support
Drug therapy	Review often home therapy Use low number of potent phosphate binders Assumption of some drugs during HD (i.e., vitamin supplements) Talk with the patients about the collateral effects and the benefit of the drugs prescribed Nursing support

HD, hemodialysis.

planned. The primary endpoint of the study was the proportion of patients with mean PTH < 300 pg/mL during the efficacy assessment phase. The study has demonstrated a superior efficacy for cinacalcet-based treatment algorithm in obtaining the targets for patients with SHPT. These findings were confirmed in other trials, where the superiority of cinacalcet + active vitamin D therapy compared to only vitamin D was also demonstrated. Of note, the analysis of safety showed a higher prevalence of adverse events in cinacalcet-based group, most of them for gastrointestinal diseases (nausea, diarrhea, and vomiting) [41]. In the EVOLVE study also, a higher achievement of biochemical parameters of MM between patients treated with cinacalcet compared to placebo was demonstrated. Nevertheless, the primary endpoint of the study (time until death, cardiovascular events) was not achieved [42]. However, more recent trials have also reported a reduction of the progression of vascular and valvular calcifications in dialysis patients treated with cinacalcet [43]. Thus, the positive and negative results, depending on endpoints, contribute to the lack of adherence to treatments.

Two big randomized study cohort trials have been recently realized to test etelcalcetide. Both were performed in HD patients and had 26 weeks of follow-up: the first (n = 1,023) aimed to compare the effect of the drug versus placebo on PTH levels [44]. The second (n = 683) tested the non-inferiority of etelcalcetide vs cinacalcet [45]. Etelcalcetide was able, and not inferior to cinacalcet, at reducing PTH levels.

Safety and adherence are two points that impact the therapy with calcimimetics. As mentioned by the reported studies, both reduction of serum Ca and gastrointestinal effects (diarrhea, vomiting, nausea) are frequently present during the treatment.

In the OPTIMA study, nausea, vomiting, and diarrhea have been responsible, respectively, for 32, 24, and 13% of the total adverse events in the cinacalcet-based therapy group. Nausea and vomiting were twice as common in cinacalcet-treated patients in the EVOLVE study, whereas hypocalcemia was 7 times more frequent. In a recent post-hoc analysis of the study, an incidence of severe hypocalcemia (Ca ≤7.5 mg/dL) was reported in the cinacalcet group, 18.4% of patients vs 4.4% in the placebo group. Severe hypocalcemia was associated with baseline higher PTH, alkaline phosphatase, and body mass index and lower Ca. Hypocalcemia was in the majority of cases self-limited [46].

The presence of diarrhea during cinacalcet treatment is probably related to the interaction between the drug, after its absorption, and the receptor present on the intestinal mucosa that impacts significantly the adherence to oral cinacalcet therapy. Even if these side effects had been reported in the etelcalcetide therapy, according to the comparative studies, cinacalcet seems to have higher rates of adverse gastrointestinal effects, mainly nausea and vomiting. It is important to underscore that comparative studies have also demonstrated a higher incidence of hypocalcemia in etelcalcetide-treated patients with respect to cinacalcet. This reflects the different interactions of the molecules with CaSR. Considering all these data, we can assume that at the moment, the use of intravenous calcimimetics might be recommended in those patients in which general compliance is poor and/or some gastrointestinal side effects are present with oral cinacalcet.

Conclusions and Future Perspectives

Despite the many possibilities of treatment, still today SHPT represents a problem in CKD patients. The data presented in this review underscore the importance of a correct management of the disease both from clinician and patient levels. In Table 2, general suggestions to improve adherence are reported. Clinicians should be conscious of the importance of the dialysis supply and of the nutritional habits of patients. In addition, they have the duty to explain clearly to patients the potential damage related to SHPT.

On the contrary, patients who are basically stressed by a chronic disease, are frequently un-motivated to further modify life-habits or take many (frequently un-tolerated) pills.

For all these reasons, SHPT therapy always needs a personalization of the therapy in all the three areas that have been addressed in this review.

In future, it is desirable to have therapies with better efficacy and general tolerability.

Disclosure Statement

The authors declare that no conflicts of interest exist.

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