INTEGRAL PHARMACOLOGICAL MANAGEMENT OF BONE MINERAL DISORDERS IN CHRONIC KIDNEY DISEASE (part I): From treatment of phosphate imbalance to control of PTH and prevention of progression of cardiovascular calcification

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ABSTRACT

INTRODUCTION: Chronic kidney disease-mineral and bone disorders (CKD-MBD), involving a triad of laboratory and bone abnormalities, and tissue calcifications, are very common and are associated with costly complications and dismal hard-outcomes.

AREAS COVERED: In two comprehensive articles, we review the most significant studies on contemporary and future pharmacological options for treatment of phosphate (P) imbalance (this part 1) and hyperparathyroidism (part 2), taking into account CKD-accelerated atheromatosis/atherosclerosis and/or cardiovascular calcification (CVC) processes.

EXPERT OPINION: Improvements in CKD-MBD require an integral approach, addressing all three components of the CKD-MBD triad. Individualization of treatment with P-binders and combinations of anti-parathyroid agents may provide the best biochemical control with the lowest incidence of undesirable effects. Isolated biochemical parameters do not accurately reflect calcium or P load or bone activity and do not stratify high cardiovascular risk patients with CKD. Initial guidance is provided on reasonable therapeutic strategies which consider the presence of CVC. This part reflects that although there is not a clear and absolute evidence, many studies point to the need to improve P imbalance while trying to, at least, avoid progression of CVC by restriction of Ca-based P-binders if economically feasible. The availability of new drugs (i.e. inhibitors of intestinal transporters), and studies including early CKD should ultimately lead to clearer and more cost/effective clinical targets for CKD-MBD.
1) INTRODUCTION

Accelerated atherosclerosis/atheromatosis and premature ageing are closely associated with chronic kidney disease (CKD) and end-stage renal disease (ESRD)\(^1\)\(^{-4}\). Consequently, CKD and ESRD are linked to an extremely important increase in mortality risk as compared with that in the equivalent general population\(^3\)\(^{-4}\). This disproportionate mortality hazard, mainly of cardiovascular origin, appears to be due to both classical and non-classical cardiovascular risk factors, including mineral and bone disorders (MBD)\(^5\)\(^{-6}\). In observational studies, various laboratory parameters such as serum calcium (Ca), phosphate (P), magnesium (Mg), alkaline phosphatase (AP), calcidiol, calcitriol, fibroblast growth factor-23 (FGF23)/klotho, and parathyroid hormone (PTH) levels have repeatedly been associated not only with bone disease and renal osteodystrophy but also with cardiovascular calcification (CVC), arterial dysfunction and, most importantly, increased morbidity and mortality, including sudden death\(^6\)\(^{-10}\). In 2005 the term CKD-MBD was coined to define a triad of laboratory and bone abnormalities and tissue (including vascular and cardiac valvular) calcifications, all of which are linked to poor hard-outcomes\(^5\)\(^{,11,12}\). Nevertheless, there is ongoing controversy regarding the clinical relevance of CVC screening in CKD patients\(^ {13,14}\), the most desirable biochemical targets and how to achieve them in order to improve hard-outcomes at a reasonable cost\(^ {5,9,12,15-19}\).

Mainly during the last decade, the increasing availability of new CKD-MBD-related treatments such as novel P-binders, vitamin D (VD) receptor activators (VDRA) and modulators of the Ca-sensing receptor (CaSR)–calcimimetics– has significantly increased our therapeutic possibilities\(^20\)\(^{-22}\). Based on the classical “trade-off hypothesis”\(^23\), now revitalized with the advent of the “phosphatonin” FGF23\(^7,23\), secondary hyperparathyroidism (SHPT) was traditionally treated with P-restricted diets, different Ca-dialysate contents, Ca-based intestinal P-binders, VD derivatives, and P removal by intensified dialysis therapy\(^5,22,24\). The appearance of sevelamer and recognition of the FGF23/klotho axis helped to lead to a review of paradigms in the pathophysiology of SHPT\(^23\)\(^{-26}\) and to increased awareness of the presence of CVC (and the need to quantify it), even in non-dialysis CKD patients\(^ {27,28}\) (Figure 1). As a result, the concept that a non-Ca-based P-binder could attenuate the accelerated progression of CVC in CKD patients as compared with Ca-based P-binders was introduced\(^28\)\(^{-30}\). It has also been suggested that avoidance of a Ca overload and other sevelamer-associated pleiotropic effects may have a positive impact on the survival of dialysis patients, but it has not been definitely proven\(^31\)\(^{-34}\). On the other hand, new VDRA and/or calcimimetics may allow a more effective control of SHPT and may also impact on the progression of CVC, potentially leading to improved survival\(^35\)\(^{-39}\) although it has not been either definitely proven\(^35\)\(^{-37,40}\).

Against this background, the purpose of this article is to provide an update on the contemporary pharmacological control of CKD-MBD, and the most recently developed drugs and therapeutic trends in the field. This first part focuses on agents aimed at the control of P imbalance and the importance of CVC progression in CKD patients, while the second part covers anti-parathyroid drugs and related issues. Other drugs initially designed to control CKD-unrelated osteoporosis (such as bisphosphonates, raloxifene, and anti-RANKL or anti-sclerostin antibodies) are beyond the scope of these reports and we refer the reader to other recent reviews\(^41\).
2) PHOSPHATE CONTROL

It is obvious that P is essential for life\textsuperscript{23}. However, there is a huge number of experimental and epidemiological studies describing that high serum P levels and/or an excessive P load are toxic, with impacts ranging from subclinical atheromatosis/atherosclerosis and CKD progression to death\textsuperscript{6,7,16,23,42–47}. Several studies have also reported that it is possible to predict cardiovascular outcomes or mortality on the basis of serum P levels even within the normal range\textsuperscript{48,49}. Several direct and indirect mechanisms by which P may be associated with endothelial, vascular and renal damage have been described, including oxidative stress, inflammation and a negative cross-talk with the renin-angiotensin system\textsuperscript{45,46,50}. The most frequent cause of hyperphosphatemia is the presence of CKD, and thereby CKD serves as a human model where if an atherogenic role for P exposure were finally to be demonstrated, drugs that reduce the P overload “could become the new statins”\textsuperscript{45}. These deleterious effects of P have also recently been dissociated from those induced by increased FGF23 or decreased klotho activities (inducing resistance to FGF23)\textsuperscript{2,23,45,51,52}.

2A) PHOSPHATE-BINDERS

Insufficient data are currently available to strongly endorse dietary P restriction as the primary intervention for the management of CKD-MBD, especially in stage 5D\textsuperscript{5,53–55}; but it is classically considered the first therapeutic step\textsuperscript{23}. Restriction of P intake (while ensuring adequate protein intake) is not easy and cumbersome, and is usually insufficient in patients with advanced CKD and dialysis patients\textsuperscript{22,56,57}. Thus, a P-binder is usually required to normalize serum P levels or to bring P “towards normality”, as recommended by different guidelines\textsuperscript{5}. Additionally, dietary restriction but also some P-binders may reduce FGF23 levels\textsuperscript{23,26,52}.

Routine dietary restrictions to control serum P in patients with CKD are usually associated with a reduction in protein intake (a manoeuver also used to delay progression of CKD to ESRD), which may, however, lead to malnutrition, protein-energy wasting, and poor survival in case of concomitant low caloric intake\textsuperscript{58,59}. Low P levels are recognized as a sign of poor nutritional status and associated with a higher mortality risk\textsuperscript{5,58}. Consequently, the hazards of controlling serum P levels by unsupervised restriction of dietary protein and mainly caloric intake may outweigh the benefits of P control and may even lead to worse survival\textsuperscript{58}. However, limited safety data suggest that dietary P restriction does not compromise nutrition in a monitored setting\textsuperscript{5,54,55}. Consequently, when targeting dietary P restriction the focus should clearly be on extra P intake (i.e. from P additives and soft drinks) not on an excessive protein restriction\textsuperscript{52,55,60}. A qualitative modification of the diet including a balanced ingestion of vegetarian compared with meat dietary protein sources (“choosing the right proteins”) and limitation of other foods with an elevated P/protein ratio is also recommended and well accepted by most patients\textsuperscript{51,62}. Supplementation with ketoanalogs constitutes a different nutritional strategy\textsuperscript{22,63}.

There is a large body of epidemiological evidence suggesting beneficial effects of P-binders and lowering serum P concentrations in dialysis patients\textsuperscript{5,9,64–66}, although there is as yet no definitive primary analysis of an interventional RCT demonstrating that any P-binder reduces morbidity or mortality\textsuperscript{31,32}. In a prospective cohort study, Isakova et al\textsuperscript{66}, comparing patients who began treatment with P-binders during the first 90 d after initiating hemodialysis (n = 3555) with those who remained untreated during that period (n = 5055), found that early
treatment was associated with a 25% lower 1-year mortality rate (HR 0.75; 95% CI 0.66-0.87; p < 0.0001). This early treatment with P-binders was independently associated with decreased mortality, not only in the intention-to-treat but also in the as-treated, and matched analyses66. Somewhat surprisingly, these results were independent of baseline and follow-up serum P levels and persisted in analyses that excluded deaths during the first 90 days of hemodialysis66. Lower adjusted hazard-ratios have also been demonstrated after adjusting for nutritional indicators65.

In a recently published multicenter, observational prospective study of 6797 European dialysis patients (COSMOS study), lower serum P and Ca levels towards the defined “safest ranges” (P 3.6-5.2 mg/dl; Ca 7.9-9.5 mg/dl) were associated with a lower relative risk of mortality using penalized splines smoothing analyses9. Previously, the use of single and combined P-binding agents was also found to be independently associated with improved survival after a 3-year follow-up64. Multivariate analyses also revealed that patients prescribed P-binders showed a 29% and 22% reductions in all-cause and cardiovascular mortality risk, respectively64. An 8% lower relative-risk of death was found for every 10% increase in the case-mix-adjusted facility prescription of P-binders64. Importantly, it was shown for the first time that, with the exception of aluminum salts, not only all single (Ca-based and non-Ca-based P-binders such as sevelamer and lanthanum) but also combined therapies were associated with better survival64. Avoidance of long-term use of aluminum-containing P-binders had previously been recommended in several guidelines6.

### 2.1.1) CLASSICAL CA-BASED vs NON-CA-BASED P-BINDERS (Sevelamer and Lanthanum)

KDIGO guidelines suggest to use “P-binding agents in the treatment of hyperphosphatemia” in patients with CKD stages 3-5 and 5D, and that it is reasonable for the choice of P binder to take into account CKD stage, presence of other components of CKD-MBD (e.g. CVC), concomitant therapies (e.g. VDRA and/or calcimimetics), and side effect profile5. Moreover, in patients with CKD stages 3-5D (dialysis and non-dialysis patients) and hyperphosphatemia, the guidelines state, “we suggest restricting the dose of Ca-based P-binders in the presence of arterial calcification [not only severe calcification as suggested in the previous 2003 National Kidney Foundation (NKF)/Kidney Dialysis Outcome Quality Initiative (KDOQI™) guidelines], and/or adynamic bone disease (ABD), and/or if serum PTH levels are persistently low”5,67. The reasons underlying these statements are (a) all P-binders are effective in lowering serum P levels, (b) the use of sevelamer or lanthanum does not adversely affect bone histology in short-term studies, and (c) compared with Ca-based P-binders, sevelamer and lanthanum may be less likely to lead to high serum Ca, lower PTH levels and ABD5,68–71. Additionally, (d) non-Ca based P-binders have been shown to attenuate progression of CVC in several studies, including randomized clinical trials (RCTs) and a recent meta-analysis29,72–75. However, these results have not been uniform76. Most importantly, it is not clear whether slowing the progression of CVC translates into improvements in hard-outcomes31,32. This statement also holds true for calcimimetics37,38,40.

In line with the findings of a previous secondary analysis of a large RCT in dialysis patients31, a survival benefit has now been described for non-Ca-based P-binders, mainly sevelamer, in small CKD dialysis and also non-dialysis populations28,77, and in two recent large meta-analyses33,78. However, these results are not completely
consistent. Moreover, the studies did not address whether non-Ca-based P-binders are inherently beneficial or whether Ca-based P-binders are harmful. As a matter of fact, in some studies Ca-based P-binders were titrated to high doses because of protocol-driven targets and extrapolation to situations of low-Ca exposure and combination therapy should be made with caution. Consequently, strong universal recommendations cannot be made.

It was recently shown that 1,500-mg/day of oral Ca carbonate induced a positive Ca balance but did not affect the P balance in predialysis stage 3-4 CKD patients under metabolic ward conditions. Questions remain as to whether these effects would persist over time and where (soft tissues or bone) and how the retained Ca load would be deposited. In another study, it was described that normal individuals and patients with late stage 3 and stage 4 CKD were in slightly negative to neutral calcium balance on an 800-mg/day Ca diet, whereas on a 2000-mg/day diet normal individuals were in modest positive Ca balance and patients with CKD were in marked positive Ca balance, at least over the 9 days of the study. It is not surprising, then, that Di Iorio et al. reported that in patients with CKD stage 3-4, moderately hyperphosphatemic in average, all-cause mortality and the composite end point of all-cause mortality and dialysis inception were lower in patients randomized to sevelamer as compared with those randomized to Ca carbonate over a period of 36 months. This study did not include a placebo-control group but, in a previous observation, total coronary Ca score was found to be significantly increased in patients following a low-P diet alone, increased to a lesser extent in Ca carbonate-treated patients, and not increased at all in sevelamer-treated patients. Nonetheless, a recent placebo-controlled RCT, in patients with CKD stage 3b-4 (mean estimated glomerular filtration rate 30-33 ml/min/1.73m²) and a mean serum P of 4.2 mg/dl, revealed an unexpected increase in CVC in CKD patients on active treatment with Ca acetate, sevelamer or lanthanum carbonate, although the increase was more pronounced in the Ca acetate subgroup. Other studies have not shown impacts of P-binder intervention on pulse-wave velocity or other markers of cardiovascular disease in non-dialysis CKD. Urgent studies are needed to solve this conundrum.

Although the potential benefits of non-Ca-based P-binders are usually attributed to a lower Ca burden and the possibly associated decrease in progression of VC and its harmful effects, other non-P-lowering effects may also be responsible for improved survival. Among other beneficial pleiotropic effects, the lipid-lowering properties of sevelamer are well documented and further positive actions have been documented on inflammation, oxidative stress, endothelial dysfunction, atherogenesis, several uremic toxins, uric acid, glycosylated haemoglobin levels and advanced-glycosylation end-products, bacterial lipopolysaccharides, Wnt/B-catenin pathway, and energy-related hormones (e.g. leptin). These effects of sevelamer, a P-binder restricted to the intestinal lumen, underline the importance of the intestinal pathway in CKD and are opening the way to new therapeutic strategies for the management of CKD and its complications. Non-Ca-based P-binders including sevelamer, lanthanum and others (see below) decrease serum FGF23 levels, and at least to a certain extent, this action may contribute to improved survival even though the FGF23 reductions are not always sustained. A better nutritional status in patients treated with P-binders and a more liberal diet cannot be ruled out as contributing factors.
2.1.2) ASSOCIATION of CA AND MG AS P-BINDERS

Low serum Mg levels are not uncommon in CKD patients and have been associated with a high cardiovascular risk and mortality\cite{87-89}. Observational studies of dialysis patients have shown that low serum Mg levels occur concurrently with mitral annular calcification, peripheral arterial calcification, and increased carotid intima–media thickness. Experimental studies have shown that Mg inhibits CVC, by both direct and indirect effects on the vessel wall\cite{87,90}. Small interventional studies suggested that long-term administration of oral Mg supplements to hemodialysis patients might retard CVC (in the absence of a control group)\cite{91}, and led to a significantly lower carotid intima–media thickness\cite{92}. Another recent pilot study randomized 72 stable hemodialysis patients to a regimen containing Mg carbonate and Ca acetate vs one containing Ca acetate alone\cite{93}. It was shown that, after a 12-month follow-up period, patients on the Mg-containing regimen had retarded CVC\cite{93}.

In spite of these findings, a beneficial role of Mg supplementation in CKD, and in particular on cardiovascular morbidity and mortality, has not been clearly demonstrated to date. Nevertheless, Mg has also been associated with a variety of positive effects: it acts on the CaSR (though less potently than Ca) and has been held responsible for anti-arrhythmic and other pleiotropic effects\cite{87}. Serum Mg levels also significantly modify the mortality risk associated with hyperphosphatemia in hemodialysis patients\cite{89}. Among patients with serum P levels of ≥6.0 mg/dL, the cardiovascular mortality risk decreased significantly with increasing serum Mg levels\cite{89}.

Consequently, despite the absence of long-term data and appropriate RCTs on hard-outcomes, contemporary combinations of Mg with low doses of Ca (MagneBind\textsuperscript{®}, Osvaren\textsuperscript{®}) may be considered as cost-effective alternatives in the treatment of hyperphosphatemia in dialysis patients unless ABD, hypercalcemia or persistently low PTH levels are present\cite{21,93,94}. They also decrease serum FGF23 levels\cite{95}. A comparison among these P-binders is shown in Table 1.

2.1.3) NEW INTESTINAL P-BINDING AGENTS:

Dietary P restriction does not usually achieve clinical goals by itself\textsuperscript{54,96}. Improper P labelling and lack of affordable healthy foods contribute to the problem\textsuperscript{52}. Actually, more than one-third of CKD dialysis patients still remain hyperphosphatemic despite all currently available treatments\textsuperscript{5}. Therefore, optimal P control is still an unmet need in CKD and the long historical search for the best possible intestinal P-binder continues\textsuperscript{20,21,56,57}. Tolerance, long-term adherence (term currently preferred to “compliance”), and clinical effectiveness are still far from ideal, in part due to the excessive pill burden and the need to be taken at meal time\textsuperscript{57,97,98}. Thus, compliance with P-binder prescription is a fact of paramount importance in attaining significant biochemical and clinical goals\textsuperscript{98,99}. It has been actually stated that the most effective P-binder yet discovered is the one that the patient will take\textsuperscript{100}. Actually, if serum P levels remain high, physicians tend to increase the prescription of P-binders, only aggravating the situation and further worsening drug adherence\textsuperscript{101}.

New galenic formulations, have been developed with the ultimate aim of improving adherence by decreasing the number of pills or by administration of palatable oral suspensions\textsuperscript{97,102}. Sevelamer carbonate [Renvela\textsuperscript{®} tablets (800 mg) or powder (800–2400 mg)] increases the dosage options and avoids the metabolic
acidity and lactuca associated with sevelamer hydrochloride (Renagel®, 800 mg)\textsuperscript{102,103}. The new lanthanum carbonate (Fosrenol®) presented as an oral powder is miscible with soft food as if it were a sort of seasoning (“salt for kidney patients”)\textsuperscript{97}.

Beyond frequent secondary effects [mainly of gastrointestinal (GI) origin], attempts to find P-binders have been fraught with problems in the form of new diseases (aluminum-based P binders), concerns about hypercalcemia and/or cardiovascular toxicity (Ca-based P-binders), concerns about tissue accumulation (lanthanum), and excessive cost (i.e. sevelamer, lanthanum)\textsuperscript{16,17,56,57}. For cultural and other reasons\textsuperscript{104}, most recent P-binders (as well as ESRD-related drugs) have been initially developed in Japan.

\subsection{2.1.3.1) COLESTILAN (MCI-196)}

Colestilan (BindRen®) has been described as a new, non-metal, non-Ca-based P binder. It is a non-absorbable anion-exchange resin which has long been used in Japan for dyslipidemia treatment. Similarly to sevelamer, colestilan binds P and bile acids in the GI tract, significantly decreasing serum P and LDL-cholesterol levels\textsuperscript{105,106}. Lower uric acid and glycosylated haemoglobin levels have also been described\textsuperscript{105–108}. Most reported adverse events have been of mild or moderate intensity, the most common being GI complaints such as nausea, vomiting and diarrhea\textsuperscript{105}. Colestilan was launched in Germany and Austria in 2013, but it is not available anymore in the European Union because of commercial reasons.

\subsection{2.1.3.2) CHITOSAN}

Chitosan (RenaGum™), released in some countries as a “medical food”, was developed as a chewing-gum that potentially binds the P contained in the 1 to 1.5 liters of saliva produced every day\textsuperscript{109,110}. As an add-on therapy to standard P-binders, it seemed to contribute very significantly in reducing serum P levels in CKD patients\textsuperscript{109}; however, despite the initial great expectations, recent randomized studies have been unable to duplicate those results\textsuperscript{110,111}.

\subsection{2.1.3.3) IRON-BASED P-BINDERS}

The effects and safety of iron-based P-binders as an alternative in the treatment of hyperphosphatemia in dialysis patients have been analyzed in a recent systematic review and meta-analysis\textsuperscript{112}. These P-binders have generally been shown to be non-inferior to sevelamer (although they lack of its pleiotropic effects) and to be relatively well tolerated. However, there are many significant differences among them, regarding P-binding chemistry, iron absorption profiles and number of pills\textsuperscript{21,113,114}. Sucroferric oxyhydroxide and ferric citrate are currently available in clinical practice in several countries\textsuperscript{21,22,56,57,113,114}. Both decrease FGF23\textsuperscript{115}, adding to the interesting new relationships described between iron and FGF23\textsuperscript{21}. Since they are Ca-free, it is not surprising that in rat models of uremia these P-binders prevent CVC\textsuperscript{116}. 
Sucroferric oxyhydroxide

Sucroferric oxyhydroxide (SFe-OOH, PA21, Velphoro®) is a new chewable and flavored Ca–free polynuclear iron-based P-binder\textsuperscript{117–119}. The binding of the P-iron complex is strong; SFe-OOH is consequently poorly soluble and it has an excellent binding capacity per prescribed unit\textsuperscript{120}. These properties allow a lower pill-burden and almost no absorption of the ferric compound as compared with ferric citrate.

The initial daily SFe-OOH dose to control hyperphosphatemia is 3 pills/day (2500 mg or 500 mg of iron/pill). Flöege et al recently reported SFe-OOH to be effective in lowering serum P in dialysis patients, with similar efficacy to sevelamer carbonate, a lower pill burden (3.1 vs 8.1), and better adherence in a short-term study\textsuperscript{118}. More treatment-emergent adverse events were described in the SFe-OOH group (45.1\% vs 33.6\% with sevelamer), but this difference was mainly due to discolored feces (15.4\% vs 0.3\%) and diarrhea (20.1\% vs 7.5\%). The serum P-lowering effect was maintained over 1-year with a lower pill burden (4.0 vs 10.1) with no evidence of iron accumulation, and the GI-related adverse events decreased over time\textsuperscript{119}. Patient adherence was 86.2\% with SFe-OOH versus 76.9\% with sevelamer\textsuperscript{119}. Additionally, a decrease in baseline mean serum FGF23 levels has been observed after 1-year of SFe-OOH, although the reduction was significantly lower than with sevelamer\textsuperscript{121}. Finally, it is worth mentioning that SFe-OOH, similarly to lanthanum, does not seem to interfere with the absorption or bioactivity of fat-soluble vitamins (such as A, D, E, and K), which may represent a difference from sevelamer and other P-binders\textsuperscript{122}. There is also a low risk of drug-drug interactions between SFe-OOH and many commonly used drugs, and SFe-OOH may therefore be administered concomitantly\textsuperscript{123}. Iron salts, but also Ca-carbonate, sevelamer, lanthanum and aluminum, among others, interfere with the absorption of oral levothyroxine\textsuperscript{124}.

Ferric citrate

Ferric citrate (Auryxia™, previously known as Zerenex®, JTT-751 or KRX-0502) is also non-inferior to active comparators (sevelamer carbonate and/or Ca acetate)\textsuperscript{125–127}. In addition, the drug delivers a significant amount of iron, resulting in significantly increases in iron stores, and lowers intravenous (iv) iron requirements and long-term erythropoietin-stimulating-agent dose, making it suitable for patients requiring iron supplementation\textsuperscript{57,126,128}. However, it has been reported that some patients exceed a desirable serum ferritin or transferrin saturation level in patients already treated with iv iron\textsuperscript{128}, and thus iron parameters should be closely monitored. Citrate may also increase aluminum absorption. Diarrhea is also frequent.

Other iron-based P-binders

Fermagate (iron-Mg hydroxycarbonate), SBR-759 (a polymeric complex of iron and starch), PT-20 (ferric-hydroxide adipate) and cross-linked chitosan iron-(III) are currently in different phases of development\textsuperscript{57,112,114,129}. Old papers
reported that iron-dextran, iron-hydroxide, and iron-saccharide also bind P effectively\textsuperscript{57}.

2.1.3.4) Bixalomer and others

Other P-binders are currently in development\textsuperscript{57}. Bixalomer, an amine-functional non-absorbable polymer recently marketed in Japan, has been shown to be useful in treating hyperphosphatemia, with fewer GI side effects (not always confirmed) as compared with sevelamer, probably due to its four times lower swelling index demonstrated in preclinical studies\textsuperscript{130}. A prospective observational study and a “double-blind, randomized, placebo-and sevelamer hydrochloride- controlled open-label, parallel group study” have recently been published\textsuperscript{130,131}.

Other new non-iron-based P-binders such as Genz-644470 have been evaluated in humans\textsuperscript{57}, whereas only preclinical data are available for the poly(allylamine) polymer TRK-390\textsuperscript{26,132}.

2.2. INTESTINAL SODIUM-P COTRANSPORTER INHIBITORS

An alternative mechanism to control serum P levels is directly blocking P absorption by means of inhibitors of the intestinal type II sodium (Na)-dependent P co-transporter (NPT2b)\textsuperscript{57,133,134}. It is known that P depleted diets and all intestinal P-binders may upregulate the intestinal NPT2b expression, leading to enhanced absorption of available intestinal P when dietary P loading is reinstated and even during P-binder intermittent treatment\textsuperscript{84,134,135}. This may explain why spikes in serum P levels with dietary P loading are seen only after a period of dietary P depletion. Thus, P-binder action may be limited by NPT2b upregulation and resultant increases in dietary P absorption when P-binders are inappropriately dosed\textsuperscript{84,134}, at least partially explaining the poor control of serum P levels in many patients. Consequently, inhibitors of the NPT2b may become not only an important alternative\textsuperscript{84,134}, but it is also possible that they could boost the P-binder individual effects as adjunctive therapy\textsuperscript{52,84,136}. A very important additional advantage is that there is no strict need to take them with meals, potentially leading to better patient adherence\textsuperscript{135}.

2.2.1) NICOTINAMIDE (NIACINAMIDE)

Nicotinamide (also known as niacinamide) is the amide of nicotinic acid (vitamin B\textsubscript{3}/niacin) and acts as a direct inhibitor of P absorption by blocking the intestinal NPT2b\textsuperscript{57,135,137}. Nicotinamide does not appear to affect Na-independent P transport and may promote phosphaturia by reducing the expression of the renal cotransporters NPT2a and NPT2c\textsuperscript{135}. Thus, nicotinamide may represent an effective and inexpensive alternative or adjunctive therapy for hyperphosphatemia in CKD patients\textsuperscript{135,136,138}.

Nicotinic acid is converted to nicotinamide in vivo and, although the two are identical in their vitamin functions, nicotinamide does not have the same pharmacological and toxic effects. Unlike nicotinic acid, the metabolite nicotinamide does not cause flushing and it is thought to be less likely to cause other adverse events related to the nicotinic acid moiety (liver test abnormalities, hyperuricemia or insulin resistance, etc.). Different secondary effects seem also to be present when using
immediate-release or extended-release forms. Concerns have been expressed regarding the potential accumulation of a by-product [N-methyl-2-pyridone-5-carboxamide (2PY)] in CKD and it has been suggested that 2PY is a potential uremic toxin. Diarrhea and thrombocytopenia are the most frequent adverse events. Although earlier findings to the contrary were reported, beneficial effects on lipid levels have been described for nicotinamide. Since nicotinic acid or nicotinamide may reduce dietary P absorption, serum P, and FGF23 levels, a novel therapeutic approach to lower serum P and FGF23 levels is being tested in the COMBINE study (The CKD Optimal Management With Binders and Nicotinamide study).

2.2.2) OTHER INTESTINAL P-TRANSPORTER INHIBITORS

Several pharmaceutical companies are currently performing preclinical studies analyzing the effect of potential NPT2 (NPT2b and/or NPT2a,c) inhibitors, distinct from vitamin B₃ derivatives. ASP3325 is currently being assessed in Phase 1 studies for the treatment of hyperphosphatemia in dialysis patients. Finally, tenapanor (also known as AZD1722 and RDX5791), a minimally systemically available inhibitor of the antiporter sodium-proton exchanger NHE3, is being evaluated in clinical trials for its potential to lower GI Na-absorption, improve fluid overload-related symptoms such as hypertension and proteinuria in patients with CKD and reduce interdialytic weight gain and intradialytic hypotension in ESRD. In preclinical studies, tenapanor has also been shown to reduce intestinal P absorption, decrease serum P and FGF23 levels, and significantly decrease cardiovascular calcifications and heart mass.

2.3) INHIBITORS OF THE FGF23 RECEPTOR (FGFR)

Toxic effects of increased FGF23 (or decreased klotho) activities have been dissociated from P-loading. The consequences of abnormal P homeostasis are evident at estimated glomerular filtration rates <70 ml/min/1.73m², long before serum P levels increase. High levels of FGF23 not only may reflect P imbalance but are also directly implicated in left ventricular hypertrophy via a klotho-independent signaling pathway. These seemingly distinct, but perhaps additive, adverse effects of P on the cardiovascular system may suggest that future interventions will need to simultaneously target P and FGF23 (and/or klotho) to reduce cardiovascular mortality. Trade-offs between FGF23 and other regulators of P metabolism could make interpretation of P balance difficult. The issue is further complicated by the fact that it is possible that P-binders may favorably affect P balance with little discernable effect on serum P levels, especially in CKD patients not yet on dialysis. The lack of a standard assay for FGF23 (and klotho) is obviously not helpful. Moreover, reducing intestinal P absorption with a P-binder does not always induce sustained reductions in FGF23 despite lower phosphaturia, suggesting that factors other than P burden may be responsible for driving increases in FGF23 in CKD patients. Similarly, it has recently been shown that P intake is not tightly linked with serum P concentrations in CKD stages 3-5, and the evidence that greater P intake, assessed by 24-h urinary P excretion, is associated with ESRD, cardiovascular disease, non-cardiovascular disease, or all-cause mortality in these patients remains incomplete. Dietary P restriction suppresses phosphaturia but does not always prevent FGF23 elevation in experimental CKD. Hence, it has again been suggested that factors other than dietary intake may be key determinants of serum P and FGF23 concentrations.
Alternative theoretical approaches to decrease the deleterious effects of elevated serum P and FGF23 levels could be based on either direct blocking of the actions of FGF23 (anti-FGF23 antibodies or FGFR-blockers) or klotho delivery. Biological agents that directly target FGF23 are in development. Animals treated with anti-FGF23 antibodies improved CKD-associated hyperparathyroidism; however, anti-FGF23 antibodies increased mortality associated with dose-dependent increases in serum Ca and P levels, and aortic calcification. These findings suggest that complete abolition and/or direct inhibition of FGF23, as a counter-regulatory hormone, without targeting the distinct adverse effects of high serum P levels is undesirable. Anti-FGF23 antibodies and FGFR-blockers could still be useful, either in combination with P-lowering therapy or in patients with ESRD without significant residual renal function. Moreover, if distinct FGFR mediate off-target effects of FGF23, it might be possible to design molecules that selectively block the undesirable effects of FGF23.

3) CONCLUSION

Improvements in CKD-MBD require an integral approach, addressing all 3 components of the CKD-MBD triad. In addition to laboratory and bone abnormalities, CVC are a prominent feature of CKD and CKD-MBD and are directly linked to dismal clinical outcomes. There is an ongoing debate on the clinical relevance of CVC, but evaluation of CVC may improve both individual risk prediction and personalization of treatment strategies. Consequently, we have shown in this article a large body of evidence describing that serum P is strongly associated with CVC, morbidity and mortality, that there is a huge accumulation of data favoring control of P overload, and that P control is currently considered one of the key issues for management of CKD-MBD.

4) EXPERT OPINION

Insufficient data are currently available to strongly endorse dietary P restriction as the primary intervention for the management of CKD-MBD, especially in stage 5D; but it has been classically considered the first therapeutic step. Restriction of P intake (while ensuring adequate protein intake) is not easy and cumbersome, and is usually insufficient in patients with advanced CKD and dialysis patients. Thus, we enforce early use of P-binders when hyperphosphatemia is present and a correct (and controlled) dietary protein restriction has already been prescribed.

According to guidelines, the choice of P-binder should be individualized (Table 2), but until more definitive studies are conducted, we favor limiting the use of Ca based P-binders as much as possible and depending on the available resources, especially in patients with ABD or low PTH levels, the elderly, diabetics, patients with CVC, and those on active VD or coumadin treatment. We have shown that there is reasonable evidence that progression of CVC can be attenuated. While acknowledging that it is as yet unproven whether such an approach helps to improve outcomes in affected patients, initiatives to control pro-calcifying mineral metabolism treatment regimens seem prudent whereas multi-interventional independent RCTs and prevention of arterial lesions at earlier-stages appear distant possibilities.

Among non-Ca-based P-binders, we highlight that the widest clinical experience, the highest number of important clinical studies, and the most pleiotropic effects have been described for sevelamer (“benchmark” in most clinical studies); nevertheless, lanthanum and
the new sucroferric oxyhydroxide display excellent P-binding capacity per prescribed unit. Lower amounts of Ca are prescribed with Mg/Ca-based P-binders and use of a combination of several P-binders is also plausible. Targeting alternative mechanisms such as inhibition of intestinal or renal transporters by nicotinamide or newly developed P-transport inhibitors may improve the important limitations of GI P-binding; however, the safety profile of these agents and long-term results remain to be seen. Although no single RCT has definitely demonstrated an improvement in hard-outcomes as a result of any CKD-MBD-related treatment (including absolute or relative reductions in serum P levels), and interesting debates persist, we favor bringing serum P levels as close to normality as reasonably possible (at least < 5.2 or 5.0 mg/dl in dialysis patients) using sound and rational measures and taking into account patient experiences.

We have shown that serum P levels may not reliably reflect P balance and that its consequences are already evident before serum P levels rise above the normal range. However, although early treatment seems to be the most desirable approach, a huge vacuum of knowledge still exists in the predialysis population without hyperphosphatemia and high FGF23 levels/phosphaturia. Consequently, primary prevention of hyperphosphatemia is still not widely substantiated; unfortunately, contradictory and unexpected results have been published in this regard, particularly if coupled with Ca loading.

We finally conclude that individualization of P-binders and reasonable combinations with anti-parathyroid agents may currently provide the best possible biochemical control with the lowest incidence of undesirable effects. P imbalance should not be separated of other laboratory parameters such as Ca, PTH, CVC and probably other cardiovascular risk factors. As pressure on health resources mounts further, attention should focus not merely on absolute costs but also on the potential health risks of drugs which may favor CVC (such as Ca-based P-binders or high doses of VDRA) and its costly associated pathology. Cheap and readily accessible means of assessing CVC, including lumbar, thoracic, pelvis and hand X-rays and echocardiography, may be of growing relevance in this context, and the recent arrival of generic P-binders will help to reduce the bill while waiting for potentially definitive studies to be done. In order to integrate all the provided information, we suggest that the reader also takes account of the expert opinion section expressed in the second part of this article. A summary is shown on Table 2.
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CONFLICTS OF INTEREST

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Article highlights

- CKD is linked to an extremely important and independent increase in morbidity and mortality
- Mineral and bone disorders (MBD) explain part of this disproportionate risk
- The term CKD-MBD was coined to define a triad of laboratory and bone abnormalities and tissue calcifications (including vascular and cardiac valvular), all of which are link to poor hard-outcomes
- Treatment of CKD-MBD requires an integral approach, addressing all 3 components of the CKD-MBD triad (including potential consideration of CVC by X-rays)
- Serum P and FGF23 are strongly associated with cardiovascular morbidity and mortality
- Avoidance of P overload and serum P control, ideally towards normophosphatemia, is one of the key issues for management of CKD-MBD
- Management of P is achieved by careful dietary P restriction, the individualized prescription of P-binders, reasonable combinations with antiparathyroid-agents, and adequate dialysis
- We favor limiting the use of Ca-based P-binders as much as possible and depending on the available resources, especially in patients with ABD or low PTH, the elderly, diabetics, patients with CVC, and those on active vitamin D or coumadin treatment
- Combination of P-binders is plausible
- Targeting alternative mechanisms such as inhibition of intestinal or renal transporters may improve clinical results
- Primary prevention of hyperphosphatemia is still not widely substantiated
- RCTs including patients with early CKD should ultimately lead to the definition of clearer and more cost-effective biochemical and clinical targets for CKD-MBD
- It is not 1A-evidence level proven whether any of these approaches helps to improve hard-outcomes in affected patients, but these regimens seem prudent to avoid iatrogenic progression of CVC whereas multi-interventional independent RCTs and earlier stage prevention of arterial lesions appear distant possibilities.

This box summarizes key points contained in the article

CKD: chronic kidney disease; MBD: mineral and bone disorders; CKD-MBD: chronic kidney disease-mineral and bone disorder; CVC: cardiovascular calcification; P: phosphate; FGF23: fibroblast growth factor 23; Ca: calcium; PTH: parathyroid hormone; RCT: randomized clinical trial
| Table 1: Comparison among classical phosphate binders |
|-----------------------------------------------|
| **ADVANTAGES** | **DISADVANTAGES** |
| **SEVELAMER**  |  |  |
| - Sevelamer hydrochloride (Renagel®) | • Toxicity free | • High pill burden |
| - Sevelamer carbonate (Renvela®) | • ↓ LDL cholesterol | • GI side effects |
| | • Other pleiotropic effects (see text) | • Potential interferences with vitamin D and vitamin K GI absorption |
| | • Powder presentation | • Normal anion gap metabolic acidosis with sevelamer hydrochloride |
| | • ↓ FGF-23 | • Cost and availability |
| | • Attenuation of the progression of VC (RCTs) | |
| | • Nominally significant survival benefits (secondary predefined analysis of RCT, meta-analysis) | |
| **LANTHANUM CARBONATE** (Fosrenol®) |  |  |
| | • Aluminum and calcium free | • GI side effects |
| | • Reduced pill burden | • Potential for tissue accumulation* |
| | • Higher P-binding capacity | • Difficulties in chewing tablets (potential need for a crusher) |
| | • Powder presentation miscible with food | • Radioopacity (interference with VC) |
| | • Radioopacity (adherence?) | • Cost and availability |
| | • ↓ FGF-23 | |
| | • Attenuation of the progression of VC | |
| **CALCIUM-MAGNESIUM** (Osvaren®, MagneBind®) |  |  |
| | • Cost-effective | • GI side effects |
| | • Decreased Ca load as compared to Ca-based P-binders | • Potential for hypercalcemia and hypermagnesemia |
| | • Pleiotropic effects (see text) | • Shorter clinical experience |
| | • ↓ FGF-23 | • Availability |
| | • Attenuation of the progression of VC | |

GI: gastrointestinal; P: phosphate; LDL: low-density lipoprotein; FGF-23: fibroblast growth factor-23; RCT: randomized clinical trial; VC: vascular calcification

*Only experimental, and not demonstrated in regular clinical use
Table 2. Summary of the treatment of secondary hyperparathyroidism and CKD-MBD

Use knowledge of VC to guide treatment of CKD-MBD, use drugs in combination, and individualize treatment.

**Phosphate (and/or FGF23) control: (P-binders)**
Achieve P levels as close to normality as possible with reasonable measures, including optimization of dialysis*
Avoid additives by all possible means.
Prioritize a balanced vegetarian vs animal dietary protein source
Limit ↑ P/protein index foods.
Prioritize P-binder prescription over unsupervised non-specific protein diet restriction.
If very high serum PTH and P levels are present, consider the possibility that P may NOT be of intestinal origin.
Personalize choice of P-binder prescription depending on:
- 1- Patient preferences
- 2- CKD stage (dialysis vs non-dialysis)
- 3- Presence/absence/degree of VC
  Avoid Ca-based P-binders in patients with hypercalcemia, low PTH levels, and/or ABD. Avoid or limit Ca-based P-binders in diabetics, patients with VC, and patients treated with coumadin.
- 4- Concomitant therapies (i.e., VDRA, calcimimetics)
- 5- Side effect profile (i.e., palatability, constipation, diarrhea)
Combination of P-binders is possible.
New P-binders may improve adherence by allowing a lower number of pills.
Inhibition of intestinal transporters may soon become an alternative or add-on therapy to improve clinical effectiveness.

**PTH control (specific anti-parathyroid treatment) (see Part II)**
Aim for iPTH levels between 2 and 5 times the upper limit of normality and avoid extremes of risk (<2X or >9X).
Treat tendencies and do not respond to minor variations in PTH.
Initial drug selection may be based on CKD stage, Ca and P levels as well as on other aspects of CKD-MBD (e.g., VC).
Cinacalcet is not approved for the treatment of secondary hyperparathyroidism in CKD stages 3-5
In CKD stage 5D, use vitamin D and calcimimetics in combination to improve efficacy with fewer secondary effects, eventually always considering the Ca and P levels
Selective VDRA (paricalcitol) may provide a wider therapeutic window, especially in those with a trend toward hypercalcemia or hyperphosphatemia, diabetic patients, and those prone to VC (experimental).
Cinacalcet is considered first-line treatment in hypercalcemic dialysis patients.
I.V. etelcalcetide may improve compliance.
CKD-MBD: chronic kidney disease-mineral and bone disorder; P: phosphate; Ca: calcium; VC: vascular calcification; ABD: adynamic bone disease; VDRA: vitamin D receptor activators; iPTH: intact parathyroid hormone; i.v.: intravenous; <2X->9X: less than 2 times or more than 9 times the upper limit of normality for the assay.

*Curiously, just in the summary of product characteristics of non-Ca based P binders it is stated that they are indicated for the control of hyperphosphatemia in adult patients with CKD not on dialysis only with serum P > 1.78 mmol/l (5.5 mg/dl).
FIGURE 1.
Legend Figure 1. Changes in therapeutic strategies for secondary hyperparathyroidism (SHPT)

(A) The pyramid reflects a classical therapeutic strategy used in the past. Treatment usually started with dietary phosphate (P) restriction, P-binders [mainly calcium (Ca)-based] and P removal by intensified dialysis therapy (increasing frequency or length of dialysis sessions). High-Ca dialysate baths were usually implemented. Increased parathyroid hormone (PTH) levels were initially treated by oral or intravenous calcitriol or alfacalcidol, and later selective vitamin D receptor activators (SVDRA, paricalcitol or maxacalcitol) and cinacalcet were added to the therapeutic armamentarium. Before the advent of new drugs, parathyroidectomy (PTX) was not uncommon. If available, renal transplantation (RT) is obviously the best option.

(B) The description of the FGF-23/Klotho axis and the highest cardiovascular risk associated with vascular calcification (VC) helped to review paradigms on the pathophysiology and consequences of SHPT, to underline the importance of chronic kidney disease-mineral and bone disorders beyond bone, and to increase awareness on the potential importance of accelerated vascular calcification (VC) and atherosclerosis progression. A combination of drugs with less feed-back interactions may help to improve control not only of laboratory parameters (with lower doses and consequently adverse effects) but also to attenuate the progression of VC and/or potentially to improve hard-outcomes. Nicotinamide is an inhibitor of the intestinal Na-P2b cotransporter (there are others in different phases of development). Native vitamin D refers to native vitamin D₂ (ergocalciferol) and vitamin D₃ (cholecalciferol), although 25-(OH)-vitamin D (calcidiol or calcifediol) is also used in some countries to increase serum calcidiol levels. FGF-23: Fibroblast growth factor 23.