

# Treatment of hyperphosphataemia and relationship with the KDOQI CKD-MBD guidelines

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## ■ ABSTRACT

Hyperphosphataemia plays a critical role in the concept of mineral and bone disorders and vascular calcification-related cardiovascular complications as the leading cause of death and most “expensive” complication in the treatment of the chronic kidney disease population. In spite of several existing sets of clinical guidelines, which do not admittedly, take into account financial considerations, the growing number of patients requiring dialysis is further pressing clinicians to justify the cost-effectiveness of their treatment.

It has become increasingly evident that calcium-based phosphate binders might substantially contribute to vascular calcification progression, particularly in patients treated simultaneously with active vitamin D derivatives. Nowadays, sevelamer is the most widely used non-calcium-based phosphate binder that reduces the risk of hypercalcaemia and vascular calcification in dialysis patients, compared with calcium-containing phosphate binders. The reported beneficial effects of sevelamer treatment from recent clinical trials have demonstrated an improved survival, and a decreased rate and duration of hospitalisation admissions compared to calcium-based binder treated patients.

On the other hand, the cost of implementation of CKD-MBD KDOQI guidelines should at least one criterion for sevelamer use be met was recently reported as being too expensive. Moreover, sevelamer use expenditure extrapolated at the national level was

estimated to be at a tremendously high, irrational level. Given the potential budgetary impact of non-calcium-based phosphate binder treatment, future nephrology clinical practice guidelines should be limited to high risk patients in terms of clinical outcomes rather than at a treatment indicated by a single mineral metabolism index. Although there is still much to be done to achieve optimum therapeutical control of mineral and bone disorders, at present clinicians should be working to “do no harm” by limiting the calcium exposure of our dialysis patients.

### Key-Words:

Hyperphosphataemia; KDOQI guidelines; calcium based phosphate binders; sevelamer; pharmaco-economy.

## ■ INTRODUCTION

The last few decades have seen a consensus over the clinically relevant definition and classification of mineral and bone disorders (MBD) in chronic kidney disease (CKD) patients. MBD is a common systemic complication developing in a clinical setting as evidenced by a combination of mineral, hormonal and bone abnormalities, as well as vascular and soft tissue calcifications<sup>1</sup>. Hyperphosphataemia is considered the main culprit in the pathogenesis of MBD in patients with advanced CKD<sup>2</sup>. In the presence of elevated calcium x phosphate (CaxP) product, with normal, or even low-normal serum calcium concentration, hyperphosphataemia contributes to an increased cardiovascular

mortality in dialysis and pre-dialysis patients through initiation and progression of vascular calcification<sup>3-5</sup>.

Although several studies have shown the compelling association between abnormalities in serum phosphate, calcium, and parathyroid hormone (PTH) levels and all-cause and cardiovascular mortality<sup>2,6,7</sup>, the major mortality risk remains in patients with phosphate levels greater than 2.3 mmol/l (7.0 mg/dL)<sup>8</sup>. Since hyperphosphataemia and disturbed mineral metabolism are recognised as an important cause of morbidity, mortality, and decreased quality of life, many currently available therapeutic strategies were proposed to control and prevent these complications.

In view of the growing body of evidence linking various treatment strategies and related clinical outcomes and in line with their goal of improving the quality of care and outcomes of patients with kidney disease, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) published their first Bone Metabolism and Disease treatment guidelines<sup>9</sup> in October 2003. Since these and other medical guidelines are generally graded according to their evidence level, the authors of the guidelines acknowledged that additional evidence from observational and randomised clinical trials is needed to complete future revisions to these guidelines. Indeed, the low evidence judgements presented in the guidelines are generally perceived to be as much absolute truth by the medical community as are high evidence guidelines<sup>10</sup>.

Aware of this bias and existing evidence on the newer therapeutics and related clinical outcomes, the KDIGO initiative has recently launched the new guidelines on CKD-MBD<sup>11</sup>. This editorial reviews some data on previous KDOQI guidelines related outcomes, adoption strategies ensuing from pharmaco-economy driven difficulties in various health care policies, and shortcomings in their implementation.

## ■ IMPLEMENTATION OF GUIDELINES – WHAT SHOULD WE LOOK FOR?

### ■ Indicators of bone and mineral disorders and associated morbidity and mortality

KDOQI guidelines contain recommended treatment target ranges for PTH (150 to 300 pg/ml), Ca

(particularly the lower end from 2.1-2.4 mmol/l (8.4 to 9.5 mg/dl), P 1.1-1.8 mmol/l (3.5 to 5.5 mg/dl), CaxP <4.4 mmol<sup>2</sup>/l<sup>2</sup> (55 mg<sup>2</sup>/dl<sup>2</sup>), as well as management strategies to achieve these goals<sup>9</sup>.

Nowadays, the recommended control of mineral metabolic parameters is still an elusive goal for many individuals on long-term renal replacement therapy<sup>7,8,12</sup>. One of the difficulties in achieving multiple KDOQI targets consistently is that most existing standard treatment approaches reflect a compromise between controlling PTH and controlling Ca and P. A few studies have reported the percentage of patients who had all four criteria (Ca, P, CaxP product and PTH) within the range simultaneously as very low (up to 10 %)<sup>12-15</sup>.

This value might be partially explained by the type of prescribed phosphate binders. Non-calcium-containing phosphate binders were not yet available during the greater part of these study periods, and the majority of patients were administered calcium-based phosphate binders (calcium acetate or calcium carbonate). Therefore, the observed high plasma calcium concentrations could have been caused by the use of calcium-containing phosphate binders, which in turn might have depressed PTH levels.

Nevertheless, there was a small, but noticeable effect in achievement of the prescribed target levels after publication of the guidelines. A few studies reported a decrease in serum calcium levels, which the investigators attributed to diminishing use of calcium-based phosphate binders and a decrease in dialysate calcium concentrations<sup>16-18</sup>. However, the potential adverse effects of calcium overload must be weighed in each case against the potential risks of PTH increases, particularly if calcimimetics are not available<sup>19</sup>. Furthermore, it is also important to have a consistent control of Ca, P, and PTH values within the KDOQI target range as it was recently reported that a 90-d period of consistent control of all markers was associated with lower mortality<sup>20</sup>. In addition, sustained achievement of each target over time and/or simultaneous control of greater number of mineral markers within the KDOQI proposed targets were associated with improved survival compared with controlling fewer markers in a shorter duration<sup>21</sup>.

Finally, although application of the KDOQI guidelines allows for a better achievement of the KDOQI targets, it does not always appear to be sufficient to overcome all

difficulties arising in daily management of real patients who obviously need a more individual approach.

### ■ Type of treatment for hyperphosphataemia and related outcomes

The management of hyperphosphataemia and MBD markers might be evaluated through various surrogate clinical endpoints such as vascular calcification and bone disease, or hard clinical outcomes like cardiovascular events. According to the recent position statement on behalf of the Portuguese Society of Nephrology on the treatment of CKD-related MBD, the effect of lowering phosphate levels should be evidenced only through the beneficial patients' clinical outcomes such as mortality, cardiovascular events, hospital admission and bone fracture<sup>22</sup>. Nowadays, some newer therapies (*e.g.*, Renagel<sup>®</sup> and Renvela<sup>®</sup> [Genzyme Corporation, Cambridge, MA]; (Fosrenol<sup>®</sup> [Shire Pharmaceuticals, Hampshire, UK]; Sensipar<sup>®</sup> and Mimpara<sup>®</sup> [Amgen, Inc., Thousand Oaks, CA]), as well as combinations of therapeutic agents, may be used to facilitate the achievement of consistent control of multiple MBD parameters and beneficial outcome data<sup>23</sup>.

What is the real evidence? Although it is important to consider the limitations of data generated from meta-analyses<sup>24</sup>, the sole systematic review comparing sevelamer to any other therapy could not find convincing evidence that sevelamer improves clinically relevant outcomes in ESRD patients<sup>25</sup>. Nevertheless, the available data on mortality benefit with sevelamer treatment has recently emerged and includes the following observations.

In a relatively small trial (127 subjects), Block *et al.*<sup>26</sup> demonstrated a survival benefit (as a secondary endpoint) in incident dialysis patients receiving sevelamer *versus* calcium-containing binders. On the other hand, the largest outcome study ever conducted in the prevalent dialysis population (Dialysis Clinical Outcomes Revisited – DCOR) could not show a difference between sevelamer and calcium based binder treatment in all-cause mortality in the overall population<sup>27</sup>. However, in a pre-specified subgroup analysis of older population (age >65 years) and in patients treated with sevelamer for more than 2 years, sevelamer treatment was associated with a lower all-cause but not car-

diovascular mortality. The inconsistent findings of these two studies are potentially related to the differences in the study designs (age, diabetes, dialysis duration, type of the study population – incident *vs.* prevalent) and the shorter follow up in the DCOR trial. Furthermore, in a secondary analysis of the DCOR study, there was evidence that sevelamer treated patients were less frequently (11%) admitted to hospital and spent less time (12%) in hospital<sup>28</sup>.

On the other hand, reported data on lanthanum carbonate and cinacalcet are scarce. Despite all beneficial evidence on various surrogate clinical endpoints (vascular calcification and bone disease), hard outcomes data for lanthanum carbonate treatment are limited. Wilson *et al.*<sup>29</sup> presented a *post hoc* survival analysis including patients from a previously published 2-year, comparator-controlled, safety study of lanthanum carbonate *versus* standard therapy. Although there was no significant difference in overall mortality, in a subgroup analysis survival was significantly improved in patients aged >65 years treated with lanthanum carbonate compared to standard therapy. This finding was similar to that of the DCOR study.

Concerning the availability of the data on cinacalcet, evidence exists only in terms of the successful control of KDOQI targets. Namely, two recent studies reported an improved achievement of the CKD-MBD recommended targets in dialysis patients with moderate to severe secondary hyperparathyroidism on combined therapy with cinacalcet and low doses of vitamin D sterols, without any adverse effect and with lower doses of phosphate binders<sup>30,31</sup>.

### ■ Controversy surrounding the cost effectiveness of the KDOQI CKD-MBD recommended treatment

In spite of several existing sets of clinical guidelines for CKD-MBD treatment, which do not admittedly take into account financial considerations, there is still a lot of controversy surrounding this issue in terms of advanced medical and/or budgetary evaluation. Namely, while these guidelines represent a major step forward in improved cardiovascular prevention in CKD patients, precautionous interpretation of the successful guidelines implementation and

related cost-effective analysis is obscure. Indeed, the growing number of patients requiring dialysis and especially the expensiveness of CKD-MBD treatment itself are pressing clinicians to pharmaco-economically justify the management of hyperphosphataemia with the new drugs available on the market and related outcomes.

As KDOQI guidelines have advocated the use of sevelamer across a range of common clinical scenarios in CKD<sup>9</sup>, it has been demonstrated that control of serum phosphate levels with this newer non-calcium-based binder is associated with reduced risk of death<sup>27,28</sup>. However, since sevelamer is significantly more costly than the calcium-based salts, its widespread utilisation remains controversial, exceeding what would usually be considered a good value for money<sup>32</sup>. In this regard, the large Canadian study determining the cost of implementation of KDOQI guidelines in 222 (53%) patients meeting at least one criterion for sevelamer use revealed that the yearly cost, estimated at around \$500,000, is against compelling adoption of the KDOQI recommendations<sup>33</sup>.

Thus, if non-calcium-based safer alternatives are clearly more expensive, the question is how should we proceed? It appears reasonable to control MBD markers by trying to achieve as first line approach a subtle balance in the correction of hyperphosphataemia with a low dose of calcium-based binders (1-2 g/day), fine-tuned with the use of vitamin D, various calcium dialysate concentrations, and/or a low amount of aluminum hydroxide (0.4-0.8 g/day) exceptionally, in cases of severe hyperphosphataemia<sup>23</sup>. On the other hand, adoption of the non-calcium-based binders should always be reserved in patients with abnormal values of mineral metabolism indices and increased cardiovascular risk, unless there are no economical restraints for their long-term use.

In summary, although application of the KDOQI guidelines allows for a better achievement of KDOQI targets, there is a gap between theory and practice. Clinical guidelines, designed to help resolve this complex problem, do not appear to be sufficient to overcome all difficulties arising in daily management of real patients. As recently proposed by Spiegel and Block<sup>34</sup>, the decision process from the clinician's perspective should be to "do no harm" by working

to limit the calcium exposure of our dialysis patients. Finally, there is still much to be done to achieve optimum therapeutical control of mineral and bone disorders.

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## References

1. Moe S, Drueke T, Cunningham J, *et al.* Kidney Disease: Improving Global Outcomes (KDIGO). Definition, evaluation, and classification of renal osteodystrophy: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006;69:1945-1953
2. Spasovski G, Massy Z and Vanholder R. Phosphate metabolism in CKD – from pathophysiology to clinical management. *Sem Dial* 2009 (*in press*)
3. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie G, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol* 2004;15:2208-2218
4. Menon V, Greene T, Pereira AA, *et al.* Relationship of phosphorus and calcium-phosphorus product with mortality in CKD. *Am J Kidney Dis* 2005;46:455-463
5. Kestenbaum B, Sampson JN, Rudser KD, *et al.* Serum phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol* 2005;16:520-528
6. Stevens LA, Djurdjev O, Cardew S, Cameron EC, Levin A. Calcium, phosphate, and parathyroid hormone levels in combination and as a function of dialysis duration predict mortality: Evidence for the complexity of the association between mineral metabolism and outcomes. *J Am Soc Nephrol* 2004;15:770-779
7. Young EW, Albert JM, Satayathum S, *et al.* Predictors and consequences of altered mineral metabolism: The Dialysis Outcomes and Practice Patterns Study. *Kidney Int* 2005;67:1179-1187
8. Tentori F, Blayney MJ, Albert JM, *et al.* Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 2008;52:519-530
9. National Kidney Foundation. K/DOQI, NKF: clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003;42:S1-S201
10. Zoccali C, Abramowicz D, Cannata-Andia JB, *et al.* European best practice quo vadis? From European best practice guidelines (EBPG) to European renal best practice (ERBP). *Nephrol Dial Transplant* 2008;23:2162-2166
11. KDIGO. KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Available at: [http://www.kdigo.org/clinical\\_practice\\_guidelines/kdigo\\_guideline\\_for\\_ckd-mbd.php](http://www.kdigo.org/clinical_practice_guidelines/kdigo_guideline_for_ckd-mbd.php)
12. Al Aly Z, Gonzalez EA, Martin KJ, Gellens ME. Achieving K/DOQI laboratory target values for bone and mineral metabolism: An uphill battle. *Am J Nephrol* 2004;24:422-426
13. Young EW, Akiba T, Albert JM, *et al.* Magnitude and impact of abnormal mineral metabolism in hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 2004;44(Suppl 3):34-38
14. Wei M, Taskapan H, Esbaei K, *et al.* K/DOQI guideline requirements for calcium, phosphate, calcium phosphate product, and parathyroid hormone control in dialysis patients: can we achieve them? *Int Urol Nephrol* 2006; 38:739-743
15. Noordzij M, Korevaar JC, Boeschoten EW, *et al.* The Kidney Disease Outcomes Quality Initiative (K/DOQI) Guideline for Bone Metabolism and Disease in CKD: Association with mortality in dialysis patients. *Am J Kidney Dis* 2005;46:925-932

16. Arenas MD, Alvarez-Ude F, Gil MT, *et al.* Application of NKF-K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease: Changes of clinical practices and their effects on outcomes and quality standards in three haemodialysis units. *Nephrol Dial Transplant* 2006;21:1663-1668
17. Wald R, Tentori F, Tighiouart H, *et al.* Impact of the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Bone Metabolism and Disease in a Large Dialysis Network. *Am J Kidney Dis* 2007;49:257-266
18. Spasovski G, Gelev S, Sikole A, *et al.* Improvement of Bone and Mineral Parameters Related to Adynamic Bone Disease by Diminishing Dialysate Calcium. *Bone* 2007;41:698-703
19. Arenas MD, Alvarez-Ude F, Torregrosa V, *et al.* Consequences of the implementation of "K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease" in a population of patients on chronic hemodialysis. *J Nephrol* 2007;20:453-461
20. Tentori F, Hunt WC, Rohrscheib M, *et al.* Which targets in clinical practice guidelines are associated with improved survival in a large dialysis organization? *J Am Soc Nephrol* 2007;18:2377-2384
21. Danese MD, Belozeroff V, Smirnakis K, Rothman KJ. Consistent control of mineral and bone disorder in incident hemodialysis patients. *Clin J Am Soc Nephrol* 2008;3:1423-1429
22. Adragao T, Ferreira A, Frazao JM, *et al.* Expert panel appraisal of the treatment of chronic kidney disease-related mineral and bone disorders (CKD-MBD): an opinion-based approach. *Port J Nephrol Hypert* 2009;23:37-42
23. Spasovski G. New strategies in treatment of mineral and bone disorders and associated cardiovascular disease in patients with chronic kidney disease. *Recent Patents Cardiovasc Drug Discov* 2008;3:222-228
24. Farkouh ME, Fuster V. Meta-analysis of small trials: proceed with caution. *Nat Clin Pract Nephrol* 2008;4:115
25. Tonelli M, Wiebe N, Culleton B, Lee H, Klarenbach S, Shrive F, Manns B; Alberta Kidney Disease Network. Systematic review of the clinical efficacy and safety of sevelamer in dialysis patients. *Nephrol Dial Transplant* 2007;22:2856-66
26. Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. *Kidney Int* 2007;71:438-441
27. Suki WN, Zabaneh R, Cangiano JL, *et al.* Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. *Kidney Int* 2007;72:1130-7
28. St Peter WL, Liu J, Weinhandl E, Fan Q. A comparison of sevelamer and calcium-based phosphate binders on mortality, hospitalization, and morbidity in hemodialysis: a secondary analysis of the Dialysis Clinical Outcomes Revisited (DCOR) randomized trial using claims data. *Am J Kidney Dis* 2008;51:445-54
29. Wilson R, Zhang P, Pratt R. Analysis of survival in a 2-year comparative study of lanthanum carbonate and standard therapy. Poster presented at the World Congress of Nephrology, Milan, Italy, 22-26 May 2009
30. Arenas MD, Alvarez-Ude F, Gil MT, *et al.* Implementation of 'K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease' after the introduction of cinacalcet in a population of patients on chronic haemodialysis. *Nephrol Dial Transplant* 2007;22:1639-1644
31. Block G, Zeig S, Sugihara J, *et al.* Combined therapy with cinacalcet and low doses of vitamin D sterols in patients with moderate to severe secondary hyperparathyroidism. *Nephrol Dial Transplant* 2008;23:2311-2318
32. Manns B, Klarenbach S, Lee H, *et al.* Economic evaluation of sevelamer in patients with end-stage renal disease. *Nephrol Dial Transplant* 2007;22:2867-2878
33. White CA, Jaffey J and Magner P. Cost of applying the K/DOQI guidelines for bone metabolism and disease to a cohort of chronic hemodialysis patients. *Kidney Int* 2007;71:312-317
34. Spiegel DM and Block GA. Should we be using calcium-containing phosphate binders in patients on dialysis? *Nat Clin Pract Nephrol* 2008;4:118-119

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