Reviewer’s report

Title: Hyperphosphatemia in CKD: assessing the current evidence linking outcomes with treatment adherence

Version: 1 Date: 25 March 2013

Reviewer: Vincenzo Bellizzi

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In this manuscript Dr Covic and Dr Rastogi present a review examining the relationship between poor serum phosphate control and outcomes in ESRD patients and consider possible strategies to improve phosphate control, mainly by increasing adherence to phosphate binders. The topic is interesting and of some clinical relevance, but some concerns have to be discussed.

Major

1. The Authors in the review refer to CKD but almost all references (but #Ref 9, 25 and 33) relate to dialysis patients and evidences on CKD not in dialysis are very scarce; this is mainly true for outcome where safety and efficacy of PB in CKD remain uncertain and further data evaluating the relation with survival are needed. Refer to CKD in the whole is misleading since CKD not in dialysis and ESRD differ for levels, targets and removal of phosphate, the outcomes related to phosphate are diverse and also the treatment is different. Authors should discuss only the ESRD along the entire paper, modifying the terminology used in the paper and eliminating the citations on CKD not in dialysis (Title, abstract, pg4, etc.).

2. A strong message from the paper (pg 5) is that diet is inadequate to obtain the serum phosphate control and, on the contrary, it is dangerous because of the risk of malnutrition; as a result, PB alone can obtain the control of serum phosphate while allowing nutritional freedom. This paradigm is not fully true. The statement that the dietary restriction of phosphate is insufficient to maintain the phosphate control is based on #Ref 15 which, however, discusses on pharmacological options to treat CKD-MBD, but not diet; nevertheless, this is somewhat true (i.e. dietary restriction by alone) in dialysis, but not in CKD. On the other hand, as stated in #Ref 17, in dialysis patients a protein intake greater than 1.0 g/kg/day is sufficient to maintain adequate nutrition, but mortality decreases when protein intake increases up to 1.4 g/kg/day despite of higher serum phosphate; therefore, the relation between intakes of protein and phosphate and the outcome is a little more complex. A further concern is the binding power of PB; the Lanthanum carbonate 1 gr. was found to bound 135 mg of phosphate whereas the Sevelamer carbonate 2.4 gr. bounds 63 mg (AJKD 2011; 57(5):700-706). Since a diet containing 1.2 g/kg/day provide to absorb around 800 mg phosphate daily (i.e. 5600 mg/week), and a single hemodialysis session eliminates around 600 mg phosphate (i.e. 1800/week), the net daily P positive balance is around 540 (almost two fold than the amount cited on pg 9, 257 mg), which requires at least...
4 Lanthanum and 8 Sevelamer; furthermore, the higher protein intakes (usual) and the hidden phosphorus make the amount of needed PB enormous. The conclusion is that none works well by alone. The Authors should, again, limit the discussion to dialysis patients and further deepen this point, possibly adding a paragraph analysing the available dietary options in seeking to control hyperphosphatemia (kinds of proteins; vegetable, inorganic and hidden phosphorus; phosphate to protein ratio; cooking modalities – i.e. C-JASN 2010; 5:683-692; J Ren Nutr 2011; 21(4):303-8; Semin Nephrol 2013; 33(2):180-90) and providing in the paper a more equilibrate balance between dietary choices and binders options.

Other
3. The recommended ranges for target phosphate levels should be more clearly discussed.

4. On pg 3, the phrase “Additional studies published after the systematic review …” refer to #Ref 6 and 7 which, however, have been published before the discussed systematic review.

5. On pg 4, the phrase “… a threshold level of phosphate load …” does not sounds good; may be it would be “… a threshold level of serum phosphate load …”.

6. On pg 4, the #Ref 10 refers to anemia and seems not pertinent to the discussion.

7. On pg 4, the #Ref 14 discusses of dialysis and not of stage 5 CKD patients; also, in this paper a relation between phosphate levels and outcome has not been found. The Authors should clarify these points considering that the topic of the paragraph is the outcome.

8. Table 2: I suggest: to add in the title “… to improve dietary phosphorus intake and …”; to move up at the top of the list the section “patient education”, adding a further line, i.e.: “guide to food choice and cooking modalities”; the section “supportive care” is very speculative and not supported by data to be included into the table.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests

Vincenzo Bellizzi