



Beyond the phosphate binding effect of sevelamer; bright pleiotropic properties in renal failure and dialysis patients

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Three main mechanisms are responsible for hyperphosphatemia, firstly an impaired renal phosphate excretion due to acute or chronic renal insufficiency, secondly a massive acute phosphate load, and finally a primary increase in renal phosphate reabsorption (1-3). Hyperphosphatemia in chronic renal failure is related with increased cardiovascular mortality and morbidity. Lowering the phosphate load and maintaining serum phosphorus levels within the normal value are important therapeutic aims to improve clinical outcomes in chronic renal failure patients (1-3). Treatment comprises of lessening intestinal phosphate absorption by a low phosphate diet and phosphate binders. In end-stage renal failure patients on hemodialysis, phosphorus will remove during hemodialysis (2-4). While, dietary limitation of phosphorus maintaining adequate protein intake is not adequate to control serum phosphate levels in most chronic renal failure patients, hence, the prescription of a phosphate binder is necessary (1-5).

Hyperphosphatemia, a frequent and serious complication of end-stage renal disease. Phosphate retention happens early in the course of kidney failure is found to be the principal abnormality of secondary hyperparathyroidism (2-5).

Secondary hyperparathyroidism is a frequent complication of chronic renal failure and is indicated by abnormalities in serum phosphate, parathyroid hormone (PTH) and calcium concentrations, and also by perturbation in vitamin D metabolism and bone turnover. Secondary hyperparathyroidism is correlated with increased cardiovascular disease, vascular calcifications and total mortality (2-6).

While phosphate lowering is an integral feature of chronic renal failure management, the efficiency and safety of phosphate binders in of special importance (3-7). In fact, phosphate binder treatment for hyperphosphatemic dialysis patients and hyperphosphatemic stage 3–5

■ Implication for health policy/practice/research/medical education

In addition to its labeled property of serum phosphate reduction in hemodialysis individuals, sevelamer may have further effects on factors influencing vascular endothelium, like inhibition of progression of vascular calcification, reduction of fibroblast growth factor 23, abolishing of circulating inflammatory and oxidative molecules, reducing of total and LDL cholesterol, uric acid, and uremic toxins. Also sevelamer may reduce blood absorption of advanced glycation end products and endotoxins from the intestine. Hence, it is affordable to suggest that endothelial pleiotropic effects of sevelamer may have related to the diminished mortality observed in various studies.

chronic renal failure patients decreases cardiovascular risk in kidney disease (1-7).

Indeed, there is a tendency toward using a phosphate binder in an effort to improve efficacy or to minimize side effects of binders (2-7).

Aluminium-containing substances are efficient however no longer widely used because of their toxicity. Calcium-based salts are effective, most widely used and inexpensive, but there is currently concern about their subsequent hypercalcaemia, adynamic bone disease, vascular calcification and parathyroid gland suppression (4-8).

The average daily dose of calcium acetate or carbonate prescribed to control hyperphosphatemia in hemodialysis patients ranges between 1.2 and 2.3 g of elemental calcium. These doses are greater than the recommended dietary calcium intake and may result to a positive calcium balance and should probably be avoided due to adverse effects of such positive calcium balance in hemodialysis patients (1-8).

On the other hand, a non-calcium-based binder such as

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lanthanum carbonate or magnesium salts can be added when large doses of binder are required. Each of these compounds is as efficient as calcium salts in lowering serum phosphorus levels depending on an adequate prescribed dose and adherence of the hemodialysis patient to treatment (3-8).

Sevelamer is a metal-free, non-absorbed polymeric anion exchange resin phosphate binder. Sevelamer is the solitary non-calcium-containing phosphate binder that does not have potential for systemic accumulation. It binds to other elements in the gut such as bacterial endotoxins, bile acids, and advanced glycation end-products leading to various pleiotropic properties specific to a polymeric phosphate binder (3-7). Two formulations exist in the market; sevelamer hydrochloride and sevelamer carbonate. Sevelamer carbonate has been found to lower serum phosphate to the same extent as sevelamer hydrochloride, however, it is associated with higher bicarbonate levels and less acidosis. It is believed that, the polymeric nature of sevelamer and its capability to bind not only phosphate but also other molecules in the small intestine determine its pleiotropic effects (2-8).

The detection of reduction of early dialytic cardiovascular mortality and morbidity with sevelamer hydrochloride may have several possible mechanisms: not only related to lowering of serum phosphate, lipids, but also by reduced vascular calcification and inducing anti-inflammatory and anti-uremic properties (3-9).

Various investigations suggest that sevelamer may also be associated with less progression of coronary artery and aortic calcifications than calcium-based binders in hemodialysis patients. To explain of this potency for sevelamer, it should be remembered that, various situations such as hypertension, hyperuricemia, diabetes, hyperlipidemia, resulting reactive oxygen species and advanced glycation end products contribute to endothelial dysfunction and injury to vascular smooth muscle cells (3-7). Endothelial dysfunction subsequently leads to vascular pathologic processes like, vasoconstriction, lipid deposition, vascular smooth muscle cell growth, leukocyte adhesion, apoptosis and thrombosis. Recent investigations suggest that sevelamer may have additional influences on factors affecting vascular endothelium, like, lowering of total and LDL-C, inhibition of progression of vascular calcification, reduction of circulating inflammatory and oxidative molecules, uric acid, reduction of FGF-23, which its elevation is associated with left ventricular hypertrophy, and uremic toxins, and also reduced blood absorption of AGEs and endotoxin from the gut. It is reasonable to suggest that endothelial pleiotropic properties of sevelamer can contribute to the reduced mortality detected in various investigations (4-9). Recently much attention, has been directed toward on

hyperuricemia in chronic kidney disease and dialysis patients (2-5). Hyperuricemia, reduce nitric oxide synthase activity, induce endothelial oxidative stress, and is associated with endothelial dysfunction in chronic renal failure patients. Various studies have shown that, lowering of serum uric acid with allopurinol ameliorated endothelial dysfunction in chronic renal failure patients without any change in oxidative markers (3-7).

Interestingly, Sevelamer has been found to adsorb urate ions in vitro and to lower serum uric acid in hemodialysis patients. While, treatment by allopurinol to lower serum uric acid is a frequent prescription to retard progression of chronic renal failure, the effect of sevelamer on serum uric acid also may have potential to reduce endothelial dysfunction and its consequences in chronic renal failure and hemodialysis (6-11).

Conclusion

In addition to its labeled property of serum phosphate reduction in hemodialysis individuals, sevelamer may have further effects on factors influencing vascular endothelium, like inhibition of progression of vascular calcification, reduction of fibroblast growth factor 23, abolishing of circulating inflammatory and oxidative molecules, reducing of total and LDL cholesterol, uric acid, and uremic toxins. Also sevelamer may reduce blood absorption of advanced glycation end products and endotoxins from the intestine. Hence, it is affordable to suggest that endothelial pleiotropic effects of sevelamer may have related to the diminished mortality observed in various studies.

Authors' contributions

All authors contributed to paper equally.

Ethical considerations

Ethical issues (including plagiarism, informed consent, misconduct, double publication and redundancy) have been completely observed by authors.

Conflict of interests

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References

1. Goto S, Komaba H, Fukagawa M, Nishi S. Optimizing the cost-effectiveness of treatment for chronic kidney disease-mineral and bone disorder. *Kidney Int Suppl* (2011) 2013; 3(5): 457-61.
2. Douthat WG, Castellano M, Berenguer L, Guzmán MA, de Arteaga J, Chiurchiu CR, *et al.* High prevalence

- of secondary hyperparathyroidism in chronic kidney disease patients on dialysis in Argentina. *Nefrologia* 2013; 33(5): 657-66.
3. Sonikian M, Papachristou E, Goumenos DS. Optimal use of phosphate binders in chronic kidney disease. *Expert Opin Pharmacother* 2013; 14(18): 2521-32.
 4. Thet Z, Win AK, Pedagogos E, Beavis J, Crikis S, Nelson C. Differential effects of phosphate binders on pre-dialysis serum bicarbonate in end-stage kidney disease patients on maintenance haemodialysis. *BMC Nephrol* 2013; 14: 205.
 5. Vlassara H, Cai W, Chen X, Serrano EJ, Shobha MS, Uribarri J, *et al.* Managing chronic inflammation in the aging diabetic patient with CKD by diet or sevelamer carbonate: a modern paradigm shift. *J Gerontol A Biol Sci Med Sci* 2012; 67(12): 1410-6.
 6. Vlassara H, Uribarri J, Cai W, Goodman S, Pyzik R, Post J, *et al.* Effects of sevelamer on HbA1c, inflammation, and advanced glycation end products in diabetic kidney disease. *Clin J Am Soc Nephrol* 2012; 7(6): 934-42.
 7. Draca N, Lazic R, Simic P, Dumic-Cule I, Luetic AT, Gabric N. Potential beneficial role of sevelamer hydrochloride in diabetic retinopathy. *Med Hypotheses* 2013; 80(4): 431-5.
 8. Bezzaoucha S, Pichette V, Lafrance JP, Bell R, Laurin LP, Vallée M. The role of sevelamer carbonate in increasing serum bicarbonate in hyperphosphatemic predialysis patients who have metabolic acidosis. *Int J Clin Pharmacol Ther* 2013; 51(12): 989-90.
 9. Moysés RM, Canziani ME. Sevelamer and CKD-associated cardiovascular disease: going further, but far from there. *Kidney Int* 2013; 84(3): 429-31.
 10. Covic A, Passlick-Deetjen J, Krocak M, Büschges-Seraphin B, Ghenu A, Ponce P, *et al.* A comparison of calcium acetate/magnesium carbonate and sevelamer-hydrochloride effects on fibroblast growth factor-23 and bone markers: post hoc evaluation from a controlled, randomized study. *Nephrol Dial Transplant* 2013; 28(9): 2383-92.
 11. Alam S, Hussain A, Daiwajna R, Tan J. Clinical efficacy of sevelamer hydrochloride in patients with end-stage renal disease: a retrospective study. *Singapore Med J* 2013; 54(5): 263-6.

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