



Hyperphosphatemia: a novel risk factor for mortality in chronic kidney disease

Mario Cozzolino, Paola Ciceri, Andrea Galassi

Renal Division and Laboratory of Experimental Nephrology, Department of Health Sciences, University of Milan, Milan, Italy

Correspondence to: Mario Cozzolino, MD, PhD, FERA, FASN. Renal Division and Laboratory of Experimental Nephrology, Department of Health Sciences, University of Milan, ASST Santi Paolo e Carlo, Via A. di Rudinì 8, 20142 Milan, Italy. Email: Mario.cozzolino@unimi.it.

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Cardiovascular (CV) mortality in chronic kidney disease (CKD) associate with traditional risk factors (1) including dyslipidaemia, diabetes, smoking and left ventricular mass hypertrophy. Furthermore, increasing evidence supports the role of non-traditional risk factors that associate with CV morbidity, especially vascular calcification (2). These risk factors are inflammation and altered mineral metabolism.

Arterial calcification is a common complication in CKD (2). Both atherosclerosis and arteriosclerosis (with soft-tissue deposition) are prevalent in uremic patients. Besides, it's accepted that vascular calcification associates with CV mortality. The most likely culprit behind vascular calcification appears to be mineral bone metabolism (2).

Both high- and low-bone turnover can be present in CKD (3). Reduced bone metabolism in adynamic bone disease means a loss of buffer capacity for peak calcium and phosphate exposure. Thus, either calcium or phosphate levels can fluctuate, disrupting homeostasis. On contrary, hyperparathyroidism can be a source of excess calcium and phosphate, with extra-skeletal deposition. Bone can be directly and actively involved in CV disease (2,4). Bone syntheses fibroblast growth factor 23 (FGF23) can increase left ventricular hypertrophy, thus has a direct effect on the myocardium (2). In early stages of CKD, the increase in FGF23 occurs earlier than increases in phosphate or PTH levels (4,5); hence, FGF23 has been proposed as an early biomarker of phosphate overload. In later stages of CKD, FGF23 greatly increases, along with phosphate and PTH

levels, eventually peaking during dialysis (5). Elevations in FGF23 correlate with left ventricular hypertrophy (6).

Clinically, FGF23 has a direct dose-response relationship with congestive heart failure and atherosclerosis (2,7,8). This means that higher FGF23 levels are associated with a higher incidence of these CV outcomes (8).

Hyperphosphatemia *per se* causes vascular calcification and endothelial dysfunction (7). *In vitro* high phosphate exposure of vascular smooth muscle can transform the cells into osteoblasts (9). In aspect of survival rates, phosphate also exhibits a dose-response relationship, with the best survival occurring in those with phosphate below target levels (10).

To sum up, rise and fall of phosphate and FGF23 levels depend on the glomerular filtration rate and dialysis treatment. Worsening kidney disease is related to increasing serum FGF23 and phosphate levels (11).

The understanding of the role of phosphate in bone metabolism has changed (12,13). Phosphate directly increases PTH and parathyroid hyperplasia (14). It is becoming much clearer that phosphate is the driving force behind overall bone metabolism, and phosphate is becoming the central issue in CKD-MBD.

Recently, the 3Ps hypothesis for CKD was developed (12). This hypothesis deals with major risk factors for renal failure progression in CKD. The three Ps are: blood pressure, proteinuria and phosphate. With these 3Ps present in CKD patients, along with hypercalcemia, a 'perfect storm' of risk

factors causes accelerated ageing and vascular calcification. These risk factors push vascular smooth cells to transform into osteochondro-genic cells (12).

With multiple options for the control of hyperphosphatemia, concern has been on agents calcium-free phosphate binders (13). Choice of phosphate binder for patients is influenced by several factors, including male gender, older age, post-menopause, low bone turnover, diabetes, inflammation and vascular/valvular calcification (13).

Calcium-free phosphate binders, such as sevelamer carbonate and lanthanum carbonate, have been able to reduce the progression of bone disease to adynamic bone among patients with CKD unlike calcium-based phosphate binders (15).

Importantly, data from the Current Management of Secondary Hyperparathyroidism: a Multicentre Observational Study (COSMOS) in CKD patients on dialysis demonstrated that, compared with no phosphate-binding agents, the use of phosphate-binding agents was associated with a lower risk of all-cause and CV mortality (16).

Recently, COSMOS' investigators assessed the influence of a 2- (midweek) or 3-day (post-weekend) dialysis interval for blood withdrawal on serum levels of CKD-MBD biomarkers and their association with mortality (17). While there were no differences in serum calcium or parathyroid hormone levels between midweek and post-weekend patients, in post-weekend patients, the mean serum phosphate levels were higher compared with midweek patients (5.5 ± 1.4 vs. 5.2 ± 1.4 mg/dL, $P < 0.001$). Furthermore, the range of serum phosphate with the lowest mortality risk [HR ≤ 1.1 ; midweek: 3.5–4.9 mg/dL (95% CI: 2.9–5.2 mg/dL); post-weekend: 3.8–5.7 mg/dL (95% CI: 3.0–6.4 mg/dL)] showed significant differences in the upper limit ($P = 0.021$). In conclusion, midweek and post-weekend serum phosphate levels and their target ranges associated with the lowest mortality risk differ (17).

Interestingly, a meta-analysis demonstrated that the use of non-calcium-based phosphate binders lead to a 22% reduction in all-cause mortality in patients with CKD (risk ratio 0.78, 95% CI: 0.61, 0.98) (18).

In summary, new evidence suggests that the bone has a more central role in CKD-MBD. One of the ways which bone influences outcomes in CKD is through the production of FGF23. High FGF23 and high serum phosphate levels are directly proportional to CV events and survival. FGF23 heralds the increase in phosphate and may be an early marker for bone disease in CKD. Compared with calcium-based phosphate binders, the use of calcium-

free phosphate binders is related to a lower mortality risk.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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