Taking aim at targets*

Suetonia C. Palmer1,2, Jonathan C. Craig2,3 and Giovanni F. M. Strippoli2−5

1Department of Medicine, University of Otago Christchurch, Christchurch, New Zealand, 2Cochrane Renal Group, 3NHMRC Centre for Clinical Research Excellence in Renal Medicine, School of Public Health, University of Sydney, 4Department of Clinical Pharmacology and Epidemiology, Consorzio Mario Negri Sud, Italy and 5Diaverum Corporate Medical-Scientific Office, Lund, Sweden

Keywords: bone; guidelines; parathyroid hormone; phosphorus; secondary hyperparathyroidism

Since the mid-1990s, many studies showing increased mortality with higher serum calcium [1], phosphorus [2] and parathyroid hormone (PTH) [3] levels in dialysis-dependent patients have been reported. By 2003, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) released guidelines for mineral metabolism for all stages of chronic kidney disease (CKD) that have been influential in determining practice patterns [4]. For stage 5 CKD (estimated GFR <15 ml/min/1.73 m²), these guidelines prescribed serum targets of 16.5–33 pmol/l (150–300 pg/ml) for PTH, 1.1–1.8 mmol/l (3.5–5.5 mg/dl)

for phosphorus and 2.1–2.4 mmol/l (8.4–9.5 mg/dl) for calcium. Target ranges for serum calcium, phosphorus and PTH were developed by K/DOQI based on the available literature of the time and have been both standard practice for clinical care [5,6] and primary outcomes for research [7,8] ever since. While the majority of early reports linking mineral metabolism to survival were related to dialysis patients, subsequent observational analyses confirmed similar associations in all CKD stages [9–15], kidney transplant recipients [16] and other populations [17,18]. Given the apparent link between mineral metabolism and patient-level outcomes in CKD, an expanding pharmacetical armamentarium (vitamin D compounds, phosphate binders and calcimimetics) has become available; since publication of the K/DOQI guidelines on bone and mineral metabolism the use of these drugs has increased significantly, as have the related costs [19].

That altered mineral metabolism in CKD causes cardiovascular disease is biologically plausible. An osteoblastic phenotype in human vascular tissue [20] is actively upregulated by altered levels of phosphorus [21], PTH [22] and other stimulatory factors in uremic serum, resulting in vascular calcification [23] and potentially accelerated
cardiovascular disease [24]. Further, modest vitamin D receptor activation in experimental CKD reduces osteoblastic gene expression in vascular tissue [25], consistent with the observation that vitamin D therapy associates with improved survival in some [26,27], but not all [28], uncontrolled studies.

Notwithstanding a large body of observational data, surprisingly the fundamental questions about treating the mineral and bone disorder of CKD (CKD-MBD) [29], still remain unanswered and few if any randomized trials support the hypothesis that treatment of CKD-MBD results in improved outcomes. Do abnormal serum levels of calcium, phosphorus and PTH actually cause worse outcomes for CKD or is the relationship found in observational studies between mineral metabolism and survival confounded by unifying but unmeasured clinical characteristics? If biochemical markers do indeed cause altered outcomes, what are the correct serum targets that will improve patient survival? Are such targets to be achieved with existing or newer pharmacological interventions? Will therapeutic modification of serum calcium, phosphorus or PTH to within target ranges translate into better health for patients with CKD or are there drug-related beneficial/toxic effects independent of achievement of targets?

At present, physicians and patients are faced with complex treatment algorithms provided in guidelines and opinion pieces, which intersect with narrowly defined biochemical values, and require both therapeutic monitoring and repeated medication adjustment. The certainty that bad outcomes (death, cardiovascular events, hospitalization) in CKD-MBD can be prevented is also undermined by data from the nearly 100 existing randomized, controlled trials, many (but not all) of which do not demonstrate amelioration of these clinical endpoints with the relevant treatment [30–32]. The clinician is at a cross-road—observational studies suggest that mineral abnormalities are harmful to patients (or at least are coincidental with poor outcomes), but so far the treatments effective for normalizing biochemical parameters in CKD are yet to meet the promise of better survival.

In today’s Nephrology, Dialysis and Transplantation, Covic et al. [33] publish the results of a review of 35 observational studies (including ~250,000 CKD patients) that assess the relationship between mineral metabolism and outcomes. The review represents the first comprehensive systematic analysis of observational studies assessing numerous populations worldwide. Their analysis seems designed to determine whether clear and consistent serum cutpoints for biochemical targets can be recommended. The study reminds us that several large (>10,000 patients) retrospective studies of registry-based data are available to inform the debate. Setting aside the limitations of the current analysis for a moment, the key findings echo the messages revealed in the already published large-scale observational studies. Higher serum phosphorus levels [cut-points varied between 5 and 7.5 mg/dl (1.5–2.5 mmol/l)] were associated with increased adjusted all-cause and cardiovascular mortality. Risk estimates for all-cause mortality ranged between 1.1 and 2.47. Lower phosphorus levels [cut-points between 3 and 5 mg/dl (1–1.5 mmol/l)] were associated with increased all-cause mortality in patients requiring dialysis.

Fewer studies assessed serum calcium; some showed elevated all-cause mortality for calcium levels >10.2 mg/dl (>2.55 mmol/l) and <8.8 mg/dl (<2.2 mmol/l). Risk estimates for mortality with higher calcium levels ranged between 1.11 and 1.52. Studies reporting outcomes for PTH were limited to dialysis patients—approximately two-thirds of studies identified an increased all-cause mortality risk (risk estimate, 1.08–1.68) with higher serum PTH (although the cut-point for increased risk varied between 300 and 600 pg/ml (33–66 pmol/l)).

Testing the hypothesis that an exposure (e.g. serum phosphorus) causes disease occurrence (e.g. death) in a population (e.g. CKD) should be, but is not easily, achieved through randomized trials. Such associations are more practically examined with retrospective studies using epidemiological data gleaned from ‘convenience cohorts’ [34] where the observed groups are originally collected without deliberate, prospective plans to investigate the hypothesis that becomes tested in the research. This is most evident in CKD with analysis of large, often comprehensive and well-characterized populations of dialysis patients, such as the Dialysis Outcomes and Practice Patterns study (DOPPS), the United States Renal Data System (USRDS) and the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) programs. However, conflicting results between the observational studies themselves and between these and subsequent randomized controlled trials—such as for haemoglobin targets [35,36] or dialysis dose [37,38]—exemplify the practical difficulty of reliance on uncontrolled data for answering important intervention questions.

Multiple occurrences of ‘reverse epidemiology’ in end-stage kidney disease, such as observational linkages between obesity, higher blood pressure and higher LDL cholesterol with better survival (diametrically opposed to findings in the general population), also repeatedly illustrate the need for caution in teasing out cause and effect for putative risk factors in CKD. Existing subclinical and clinical disease highly prevalent in CKD but not in the general population may alter causal pathways between risk factors and outcomes that are not accounted for in epidemiological research. Even while relationships between serum calcium, phosphorus or PTH and survival remain statistically significant when adjusted for major confounding variables, the analyses summarized in today’s review still cannot account for the many unmeasured questions and the potentially unknown confounding variables that may actually be the true causal connection between mineral dysregulation and mortality. In the analysis of Covic et al., it is readily apparent that adjustment for confounding variables between studies was very incomplete and heterogeneous; only just over half of studies assessing the link between serum phosphorus and mortality adjusted for cardiovascular co-morbidities—increasing the possibility that associations observed between mineral parameters and survival are highly confounded (Table 3).

Certainly, observational studies are welcome hypothesis-generating tools, and their collective revision in today’s Journal is informative, but definitive guideline recommendations need to wait until the associations between serum targets and outcomes are tested in randomized
trials—where each treatment comparison (e.g. ‘lower’ versus ‘higher’ serum phosphorus target) is equally likely to incorporate measured and unmeasured covariates. This however has not been the pattern of research up to today. Soon the Kidney Disease: Improving Global Outcomes (KDIGO) working group [39] will release their guidelines, and will likely support the need to reverse current reliance on observational studies and the need to produce good quality randomized, controlled trials in this area of clinical uncertainty.

Further, in observational studies included in the present review, the exposure in any given patient to ‘dose’ of serum calcium, phosphorus or PTH varied over time, unlike in a randomized trial where the dose and duration of exposure are defined prospectively as part of the experimental protocol. Imprecise knowledge of overall exposure to serum mineral levels in available cohort studies further obscures understanding of the true relationship between exposure and selected outcomes in CKD for phosphorus, calcium and PTH.

For the nephrologist, selecting an optimal clinical range for serum calcium, phosphorus or PTH that provides the best outcomes for their patients with CKD remains as elusive, even with the current review, as before. The authors of this review have not combined observational studies of mineral targets by formal meta-analysis, citing marked heterogeneity between patients, exposures and outcomes for the included studies. Indeed, all available studies have defined different reference ranges for serum levels by which risk estimates are calculated. For example, studies identify different serum phosphorus levels as the reference category for mortality risk (4.4–5.5 mg/dl [40] versus 2.5–2.999 mg/dl [41] versus 4.0–4.5 mg/dl [42]). This approach limits, but does not prohibit the potential for combining data in meta-analysis to assess risks from differing serum levels across multiple populations. It arises from inconsistent post hoc categorization of serum levels in registry cohorts and accentuates the confusion about whether the K/DOQI guideline mineral targets are supported by observational analyses. Where study-level meta-analysis is not possible or informative, a collaborative and pooled analysis of patient-level data may help delineate the actual serum targets associated with poorer outcomes in observational studies, which can then inform randomized comparisons.

The pleiotropic effects of pharmaceutical agents for bone disease are incompletely understood. Do higher levels of serum calcium, phosphorus and PTH actually represent a treatment-resistant state, where unresponsive patients are exposed to higher doses of therapy that may be potentially harmful? Less than one-fifth of studies in the analysis adjusted for medication (vitamin D compounds or phosphate binders). Countering this hypothesis is the growing number of uncontrolled studies identifying a survival advantage for CKD patients receiving vitamin D compounds.

Would conducting a randomized, controlled trial to address the question of mineral targets be impossible? We have the haemoglobin-target trials showing that such studies are feasible and now have a strong and consistent signal from observational analyses that mineral targets may influence survival in CKD. A randomized trial of MBD-CKD targets, achieved independently of the pharmaceutical agent used, would not necessarily be attractive to potential funders including industry and may require a collaboration between the nephrology community and governmental funding bodies. Is it time for such a trial, taking aim at targets?

Historically, other risk factors (blood pressure, cholesterol) have not been assessed in specific target trials, but rather the link between their attainment and better health outcomes has been identified through the more feasible setting of pharmaceutical trials. Trials which show that modification of risk factors such as blood pressure or LDL cholesterol improves patient-important outcomes like cardiovascular events are almost entirely primarily designed to compare the effects of different pharmacological agents (or against placebo) and almost never designed to determine what target should be aimed for. The Hypertension Optimal Treatment (HOT) study is one of the very few examples of different blood pressure targets being the primary intervention [43]. In general, results of placebo controlled or head-to-head trials of pharmacological interventions are then extrapolated to generate treatment targets even though targets have not formally been evaluated. Similarly, for CKD-BMD trials, it would be more feasible to have non-target trials, which compare the effects of a drug against placebo or an active comparator, rather than randomize different levels of phosphorus or PTH.

The rationale for favouring this type of trial against treatment target trials is also that on epidemiological grounds it seems unlikely that there is a true target range but rather a need to treat with proper interventions within certain dose ranges. However, we still need trials to prove that existing interventions for the management of CKD-MBD actually improve patient-level outcomes. We await the E.V.O.L.V.E. study [44] to report on the efficacy of calcimimetics agents to reduce mortality and morbidity cardiovascular events in haemodialysis patients, but still need trials to determine the correct use of other and older medications in CKD-MBD (particularly vitamin D compounds). Recognition that the current evidence that links mineral targets to patient-centred outcomes in CKD falls short of rigorous scientific endeavour is now apparent and should motivate future well-designed trials to provide the answers about mineral targets that we are all still seeking.

Conflict of interest statement. None declared.

References
44. Clinical Trials Registry. The E.V.O.L.V.E. TrialTM: Evaluation of paricalcitol or calcitriol therapy. NE n g lJM e d