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Original Investigation

Association of Drug Effects on Serum Parathyroid Hormone, Phosphorus, and Calcium Levels With Mortality in CKD: A Meta-analysis

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Background: Serum parathyroid hormone (PTH), phosphorus, and calcium levels are surrogate outcomes that are central to the evaluation of drug treatments in chronic kidney disease (CKD). This systematic review evaluates the evidence for the correlation between drug effects on biochemical (PTH, phosphorus, and calcium) and all-cause and cardiovascular mortality end points in adults with CKD.

Study Design: Systematic review and meta-analysis.

Setting & Population: Adults with CKD.

Selection Criteria for Studies: Randomized trials reporting drug effects on biochemical and mortality end points.

Intervention: Drug interventions with effects on serum PTH, phosphorus, and calcium levels, including vitamin D compounds, phosphate binders, cinacalcet, bisphosphonates, and calcitonin.

Outcomes: Correlation between drug effects on biochemical and all-cause and cardiovascular mortality.

Results: 28 studies (6,999 participants) reported both biochemical and mortality outcomes and were eligible for analysis. Associations between drug effects on surrogate biochemical end points and corresponding effects on mortality were weak and imprecise. All correlation coefficients were less than 0.70, and 95% credible intervals were generally wide and overlapped with zero, consistent with the possibility of no association. The exception was an inverse correlation between drug effects on serum PTH levels and all-cause mortality, which was nominally significant (-0.64; 95% credible interval, -0.85 to -0.15), but the strength of this association was very imprecise. Risk of bias within available trials was generally high, further reducing confidence in the summary correlations. Findings were robust to adjustment for age, baseline serum PTH level, allocation concealment, CKD stage, and drug class.

Limitations: Low power in analyses and combining evidence from many different drug comparisons with incomplete data across studies.

Conclusions: Drug effects on serum PTH, phosphorus, and calcium levels are weakly and imprecisely correlated with all-cause and cardiovascular death in the setting of CKD. Risks of mortality (patient-level outcome) cannot be inferred from treatment-induced changes in biochemical outcomes in people with CKD. Similarly, existing data do not exclude a mortality benefit with treatment. Trials need to address patient-centered outcomes to evaluate drug effectiveness in this setting.

INDEX WORDS: Renal failure; surrogate endpoint; drug effect; biomarker; parathyroid hormone (PTH); phosphorus; calcium; outcomes; death; all-cause mortality; cardiovascular mortality; chronic kidney disease–mineral and bone disorder (CKD-MBD); phosphate binders; vitamin D compounds; calcimimetic agents; bisphosphonates; calcitonin; meta-analysis; dialysis.

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Treatment of chronic kidney disease (CKD) or its complications commonly involves modifying biological end points (such as urine protein excretion or blood pressure) with the ultimate aim of improving patient-relevant outcomes, such as survival or delaying end-stage kidney disease.[1] Biological markers have also been used widely as primary outcomes for the evaluation of drug efficacy and to accelerate regulatory approvals based on the assumption that treatment effects on these end points lead to improved outcomes that are relevant to patients.[2-4] Surrogate end points are frequently used in research and clinical practice because they are more sensitive to drug effects, occur more quickly than patient-level outcomes, and are easier to measure, reducing the complexity and duration of research and treatment. However, for a surrogate end point to be clinically meaningful, treatment effects on surrogate outcomes (such as albuminuria) need to reliably predict effects on true end points of clinical value (such as cardiovascular events). Changes in glomerular filtration rate as an end point in clinical trials in CKD have received specific attention from the US Food and Drug Administration recently.[5]

The bone disease that complicates CKD (known as CKD−mineral and bone disorder [CKD-MBD]) is one large-scale example of this practice in which correcting surrogate end points (abnormal serum parathyroid hormone [PTH], phosphorus, and calcium levels) is standard clinical practice in the belief that this reduces mortality and morbidity.[6] These biochemical end points have also been used for the purpose of regulatory approvals and the publicly funded subsidy of drugs, including phosphate binders and vitamin D compounds.[7,8] The prescribing of vitamin D compounds, phosphate binders, and calcimimetic agents to correct serum phosphorus and PTH levels in CKD is ubiquitous in routine clinical practice and suggested by global guidelines.[6] In 2010, the calcimimetic agent cinacalcet was the single most costly drug prescribed for US dialysis patients based on its ability to lower serum PTH levels.[9] Despite the extensive prescribing of these drugs and associated medication costs, there is uncertainty about their effects on cardiovascular and all-cause mortality.[10,11]

We have previously examined the association between serum PTH, phosphorus, and calcium levels and all-cause mortality in cohort studies and found no robust evidence of a strong and consistent association.[12] However, an evaluation of the link between drug effects on these surrogate biochemical end points and patient-centered outcomes in clinical trials is absent. This study evaluates the assumption that drug effects on widely used surrogate end points (serum PTH, phosphorus, or calcium levels) in men and women with CKD are correlated with drug effects on total and cardiovascular mortality within randomized trials.

METHODS

We conducted this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[13]

Data Sources and Searches

We searched existing meta-analyses published in the Cochrane Library for trials reporting interventions for CKD-MBD.[14-18] We supplemented data from existing meta-analyses by searching the Cochrane Central Register of Controlled Trials (CENTRAL) through issue 12, 2014, and MEDLINE (through January week 3, 2015) for study reports using highly sensitive search strategies designed by an information specialist without language restriction. We used the search strategies available in the original Cochrane review publications and supplemented these with a specific strategy for trials targeting specific biochemical values of serum PTH, phosphorus, and calcium (Table S1, available as online supplementary material).

Study Selection

We considered randomized studies in any language comparing any intervention for CKD-MBD or kidney transplantation−related bone disease, including phosphate binders, vitamin D compounds, calcimimetic agents, bisphosphonates, and calcitonin, to evaluate any association between drug effects on biochemical end points (serum PTH, phosphorus, or calcium) and drug effects on mortality outcomes. Inclusion criteria were the availability of reported serum PTH, phosphorus, or calcium levels at the end of follow-up or the proportion of participants achieving a specified biochemical target level in all treatment arms together with reporting of one or more mortality event during follow-up. We excluded data about children and from trials in which follow-up was shorter than 12 weeks.

Data Extraction and Quality Assessment

We defined the biochemical outcomes of interest a priori as either the end-of-treatment serum biochemical value (PTH, phosphorus, or calcium) or the proportion achieving a prespecified target range by end of treatment. The mortality outcomes of interest were all-cause and cardiovascular mortality. Data were extracted by one reviewer (V.S.) and double-checked by a second reviewer (G.d.B.). Any disagreements were resolved by discussion.

To avoid double-counting of participants in studies that evaluated a single drug intervention in 2 or more arms (eg, several doses of a single drug in 3 different study arms), we combined event data for the binary outcomes (mortality and biochemical) for all intervention arms of the same drug into a single analysis or extracted data from the highest dose treatment arm for continuous outcomes (end-of-treatment biochemical values). Risk of bias was adjudicated using standard tools generated by the Cochrane Collaboration, including the domains of sequence generation, allocation concealment, blinding of participants or investigators, blinding of outcome assessment, and completeness of outcome data.[19] We also identified reports of sponsor involvement in authorship and/or data analysis or management.[19]

Data Synthesis and Analysis

For each study, the log ratio of mean biochemical values or the log relative proportion of the study population in each arm achieving a prespecified serum target value at the end of treatment for the intervention and control arms were computed together with the respective standard errors. For all studies, the log relative risk