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Original Investigation

Abnormal Mineral Metabolism and Mortality in Hemodialysis Patients With Secondary Hyperparathyroidism: Evidence From Marginal Structural Models Used to Adjust for Time-Dependent Confounding

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Background: Hemodialysis patients with mineral and bone disorders (MBDs) have an abnormally high relative risk of death, but their absolute risk of death is unknown. Further, previous studies have not accounted for possible time-dependent confounding of the association between MBD markers and death due to the effect of markers of MBD on treatments, which subsequently may affect MBD markers.

Study Design: Multicenter, 3-year, prospective, case-cohort study.

Setting & Participants: 8,229 hemodialysis patients with secondary hyperparathyroidism (parathyroid hormone level ≥180 pg/mL and/or receiving vitamin D receptor activators) at 86 facilities in Japan.

Predictors: Serum phosphorus, calcium, and parathyroid hormone levels.

Outcome: All-cause mortality.

Measurements: Marginal structural models were used to compute absolute differences in all-cause mortality associated with different levels of predictors while accounting for time-dependent confounding.

Results: The association between phosphorus level and mortality appeared U-shaped, although only higher phosphorus level categories reached statistical significance: compared to those with phosphorus levels of 5.0-5.9 mg/dL (1.61-1.93 mmol/L), patients with the highest (≥9.0 mg/dL [≥2.90 mmol/L]) phosphorus levels had 9.4 excess deaths/100 person-years (rate ratio, 2.79 [95% CI, 1.26-6.15]), whereas no association was found for the lowest phosphorus category (<3.0 mg/dL [<0.97 mmol/L]; rate ratio, 1.54 [95% CI, 0.87-2.71]). Similarly, hypercalcemia (≥10.0 mg/dL [≥2.50 mmol/L]) was associated with excess deaths, and the highest level of hypercalcemia (≥11.0 mg/dL [≥2.75 mmol/L]) was associated with 5.8 excess deaths/100 person-years (rate ratio, 2.38 [95% CI, 1.77-3.21]) compared to those with levels of 9.0-9.4 mg/dL (2.25-2.37 mmol/L). Abnormally high parathyroid hormone levels were not associated with excess deaths.

Limitations: Possible residual confounding.

Conclusions: These results reinforce the idea that serum calcium (in addition to phosphorus) level is an important predictor of the absolute risk of death in hemodialysis patients with secondary hyperparathyroidism. *Am J Kidney Dis.* ■(■):■-■. © *2013 by the National Kidney Foundation, Inc.*

INDEX WORDS: Calcium; clinical epidemiology; hemodialysis; hyperparathyroidism; hyperphosphatemia; mineral metabolism; death; end-stage renal disease; parathyroid hormone (PTH).

Abnormal mineral metabolism associated with secondary hyperparathyroidism (SHPT) is an important complication in patients with chronic kidney disease (CKD). The systemic condition in which patients with CKD have adverse outcomes caused by this disorder is referred to as CKD–mineral and bone disorder (MBD).[1] In maintenance hemodialysis patients, abnormal mineral metabolism may be associated with mortality.[2-10] Both hyperphosphatemia and hypercalcemia are associated with higher all-cause mortality

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and higher mortality due to cardiovascular disease (CVD).[2-10] Therefore, guidelines for the treatment of CKD-MBD include ranges within which laboratory-measured markers of MBD should be controlled.[11-13]

Markers of MBD are known to be associated with high relative risks of mortality, but not with high absolute mortality. Information for absolute mortality could be used to estimate the number of deaths that can be attributed to an exposure or the number that might be prevented by treatment. In addition, few studies have focused on hemodialysis patients with SHPT for whom MBD-related treatments, including vitamin D receptor activators, phosphate binders, or calcimimetics, are indicated. Using calcimimetics can result in a higher proportion of patients staying within the Japanese guideline–specified target range for mineral-metabolism indexes,[13,14] but the effects of those drugs on the association between mineral metabolism and mortality are not known. Finally, and importantly, most studies have not considered the effect of MBD treatments on the association between MBD marker levels and mortality.[2-4,6-10] MBD treatments may be associated with survival,[15-18] so they may be an important confounder in these studies. They also can be affected by previous values of mineral-metabolism indexes, and they in turn can affect future values of those indicators. Because such "time-dependent confounders" are on the causal pathway between predictors and outcomes, commonly used methods such as time-dependent Cox regression can result in estimates of association that are biased.[19,20]

We quantified the absolute risk of mortality associated with abnormal mineral metabolism in hemodialysis patients with SHPT, immediately before and after calcimimetics became available in Japan. We used marginal structural models to evaluate the causal effect of each MBD marker on mortality, adjusting for the effects of possible time-dependent confounders such as MBD treatments.[20,21]

METHODS

MBD Outcomes Study for Japanese CKD Stage 5D Patients

The Mineral and Bone Disorder Outcomes Study for Japanese CKD Stage 5D Patients (MBD-5D) is a multicenter, 3-year, prospective, case-cohort study.[22] Clinical outcomes including all-cause and cardiovascular mortality were recorded from December 2007 to January 2011 in 8,229 maintenance hemodialysis patients with SHPT registered from 86 facilities in Japan (Fig 1). Mortality among hemodialysis patients is far lower in Japan than in Western countries. Because there are fewer semi-competing risks for death in Japan, these data can be particularly useful for evaluating associations between MBD markers and mortality.[28] Data for prescriptions and MBD-related serum markers were collected prospectively every 3 months (from visit 0 at registration to visit 12) and data for other time-dependent variables were collected every 6 months. A total of 3,276 patients were randomly selected from the whole cohort at a sampling rate of 40% (this group made up the subcohort). Data from patients who died and had been outside the subcohort were collected retrospectively. This study was approved by a central ethics committee at Kobe University's School of Medicine.

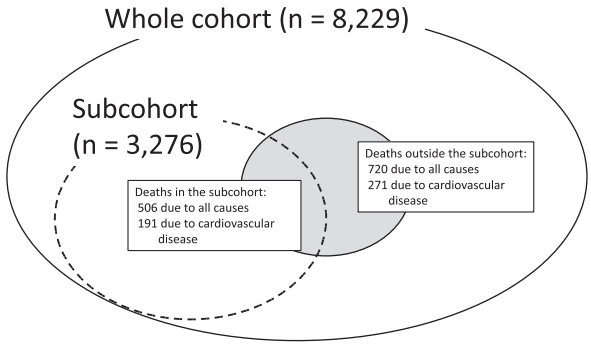

Figure 1. Case-cohort design of the Mineral and Bone Disorder Outcomes Study for Japanese CKD Stage 5D Patients (MBD-5D), showing numbers of deaths. The study has a "whole cohort" of all patients enrolled and a subcohort of a randomly selected 40% of the whole cohort. From 86 facilities, all 8,229 dialysis patients with secondary hyperparathyroidism were registered, and 3,276 were selected into the subcohort. Data were collected prospectively from the subcohort and retrospectively from those outside the subcohort who died. In total, there were 1,226 all-cause deaths and 462 deaths due to cardiovascular disease. Deaths due to cardiovascular disease comprised those due to cerebrovascular disease, heart failure, myocardial infarction, sudden death, arrhythmia, aortic disease, or other cardiovascular diseases.

Participants

The target population was made of maintenance hemodialysis patients with SHPT. To be eligible, patients must have been receiving hemodialysis at one of the participating facilities as of January 1, 2008. Eligible patients also must have either had an intact parathyroid hormone (iPTH) concentration ≥180 pg/mL (indicating a need for treatment to lower iPTH levels, according to Japan's guidelines[13]) or been receiving an intravenous (calcitriol or maxacalcitol) or oral active (falecalcitriol [the only oral activator approved in Japan for SHPT treatment]) vitamin D receptor activator. Patients who had been receiving dialysis for less than 3 months were ineligible. All eligible patients at the 86 selected facilities were registered in the whole cohort. These patients were assumed to be managed according to Japan's guidelines,[13] although the study protocol did not specify as such.

Exposures, Outcomes, and Covariates

The MBD-related serum marker levels (serum calcium, phosphorus, and iPTH) were handled as time-dependent variables (their values were updated at each visit), and their associations with clinical outcomes were examined. Levels of each marker were categorized into 8 classes, by 0.5 mg/dL of calcium, 1.0 mg/dL of phosphorus, and 100 pg/mL of iPTH. When albumin levels were <4.0 g/dL, serum calcium levels were corrected for albumin concentration by the modified Payne method, which is used commonly in Japan: corrected calcium = calcium + (4.0 − albumin).[23] Serum whole PTH levels measured with a third-generation PTH assay were converted to iPTH levels: iPTH = whole PTH × 1.7.[13]

The primary outcome was all-cause mortality. Cardiovascular mortality also was studied; it was defined as death due to cerebrovascular disease, heart failure, myocardial infarction, sudden death, arrhythmia, aortic disease, or other CVDs.