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In Practice

Dialysate Calcium Concentration, Mineral Metabolism Disorders, and Cardiovascular Disease: Deciding the Hemodialysis Bath

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Patients with end-stage kidney disease treated with dialysis are at increased risk to experience fractures and cardiovascular events than similar-aged people from the general population. The enhanced risk for these outcomes in dialysis patients is not completely explained by traditional risk factors for osteoporosis and cardiovascular disease. Mineral metabolism abnormalities are almost universal by the time patients require dialysis therapy, with most patients having some type of renal osteodystrophy and vascular calcification. These abnormalities have been linked to adverse skeletal and cardiovascular events. However, it has become clear that the treatment regimens used to modify the serum calcium, phosphate, and parathyroid hormone levels almost certainly contribute to the poor outcomes for dialysis patients. In this article, we focus on one aspect of mineral metabolism management; dialysate calcium concentration and the relationships among dialysate calcium concentrations, mineral and bone disorder, and cardiovascular disease in hemodialysis patients.
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INDEX WORDS: Dialysate calcium; cardiovascular; sudden cardiac death; calcific uremic arteriolopathy; mineral metabolism; review.

Note from Editors: This article is part 2 of a 4-part series of invited In Practice reviews highlighting issues related to the composition of dialysate.

CASE PRESENTATION

A 60-year-old woman with end-stage kidney disease had been treated with hemodialysis (HD) for approximately 1 year. She had a long-standing history of diet-controlled diabetes mellitus with stable ischemic heart disease and peripheral vascular disease. As part of the evaluation for a living donor transplant, an ankle-brachial index test was performed, revealing values of 0.19 on the left and 0.41 on the right. She subsequently underwent computed tomography, revealing extensive vascular calcification, and was deemed a poor candidate for kidney transplantation. Reviewing her medical and dialysis history, in addition to the traditional cardiovascular risk factors of diabetes, hypertension, and dyslipidemia, she had intermittent hypercalcemia with low parathyroid hormone (PTH; 15 pg/mL) and normal alkaline phosphatase levels. Her treatment regimen included calcium carbonate (900 mg of elemental calcium) with meals for phosphorus binding and dialysate calcium concentration of 2.5 mEq/L (1.25 mmol/L).

INTRODUCTION

Mineral metabolism abnormalities in patients with end-stage kidney disease treated with dialysis are associated with increased risk of fractures and cardiovascular disease. Fracture rates in dialysis patients are greatly increased compared to the general population,[1] such that an 80-year-old dialysis patient has a 2- to 3-fold greater risk of hip fracture than a similar-aged person in the general population. The greater fracture risk is also associated with higher risk of postfracture mortality.[2] Even after stratification for age, sex, race, and presence or absence of diabetes mellitus, dialysis patients have a 10- to 20-fold greater risk of death from cardiovascular disease than the general population.[3] Atherosclerotic cardiac disease is part of a much larger problem that also includes arteriosclerosis (or loss of vessel elasticity) leading to congestive heart failure and sudden cardiac death.[4,5] Risk of a cerebral vascular accident is also increased about 4- to 10-fold compared to the general population, and peripheral vascular disease is present in ∼25% of prevalent HD patients.[6,7] The prognosis for dialysis patients after myocardial infarction, cerebral vascular accident, or diagnosis of peripheral vascular disease is abysmal.[8-10] Although many dialysis patients have multiple traditional cardiovascular risk factors, the attributable risk from disordered mineral metabolism has been estimated to be 18%.[11]

The objective of this article is to review the potential contribution of dialysate calcium choice in conventional HD to the enhanced risk of mineral metabolism disorders and cardiovascular disease in dialysis patients. A recent systematic review and meta-analysis on this topic was published for intensive HD and is not discussed.[12]

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CALCIUM PHYSIOLOGY

Calcium balance is the difference between calcium intake and calcium output in a steady state.[13,14] In the general population, intake is by gastrointestinal absorption of calcium from diet; urine, feces, and sweat all contribute to calcium losses. However, calculating calcium balance is fraught with difficulties.[14,15] Dietary calcium is usually estimated from food diaries that may be inaccurate and may not take into account the effect of the different ions that calcium may be complexed with, such as phytate and oxalate. Gastrointestinal calcium absorption is affected by vitamin D status and is difficult to accurately quantify due to intra- and interindividual differences in transit time of the alimentary bolus and the obvious burden for patients and laboratory staff. Loss of calcium in sweat is also difficult to measure, but may be as high as 103 mg/d.[15] Calcium movement into and out of internal compartments is not zero, and for bone, is at least partially mediated by PTH. The bone behaves as a 2-compartment model composed of: (1) cell-mediated bone turnover in which osteoclast-initiated bone resorption and osteoblast-initiated bone reformation are tightly coupled under normal conditions, and (2) a rapidly exchangeable pool in which noncollagenous proteins such as osteonectin and osteocalcin bind or release ionized calcium and appear to acutely limit changes in serum ionized calcium concentration.[16,17]

The situation is even more complex in dialysis patients due to the variable effects of dialysate calcium (discussed later), the variable intestinal calcium absorption associated with different vitamin D analogues, the expanded internal calcium pool related to soft-tissue calcification, and the heterogeneity of the "reactivity" of the bone-exchangeable pool (Fig 1).[18-20] Even in the present era, dietary intake of calcium (not including phosphate binders) remains low at ~350 mg to 580 mg/d, of which about 20 to 175 mg will be absorbed depending on dose and type of vitamin D analogue.[18,21,22] Colonic secretion of calcium has been estimated to be 25 mmol (1,000 mg) per week.[23] Uptake of calcium by the exchangeable pool and ultimately by mineralized bone is determined by the underlying bone histology.[24] This early bone biopsy study is supported by more recent studies in which calcium mass balance was dependent on the calcium gradient, PTH level, and osteocalcin level.[25] Karohol et al[25] hypothesized that there may be an increased number of noncollagenous calcium-binding proteins at the bone surface in high-turnover bone disease that "give up" more calcium during the dialysis procedure. The efficiency with which the rapidly exchangeable pool is able to absorb/mobilize calcium also appears to be affected by serum phosphate level (less efflux), acidosis (less efflux), increased age, and diabetes mellitus.[16]

Dialysate Calcium

Early elegant studies by Wing[26] demonstrated that the change in plasma calcium level before and after dialysis did not correlate with the observed external net calcium transfer. Gain or loss of calcium by the patient depends on: (1) the inlet dialyzer diffusion concentration gradient (difference between the patient's ionized calcium level and the dialysate calcium concentration), (2) amount of ultrafiltration (hemoconcentration of plasma proteins and calcium removal), and (3) activity of the bone exchangeable pool. The potential contribution from soft-tissue

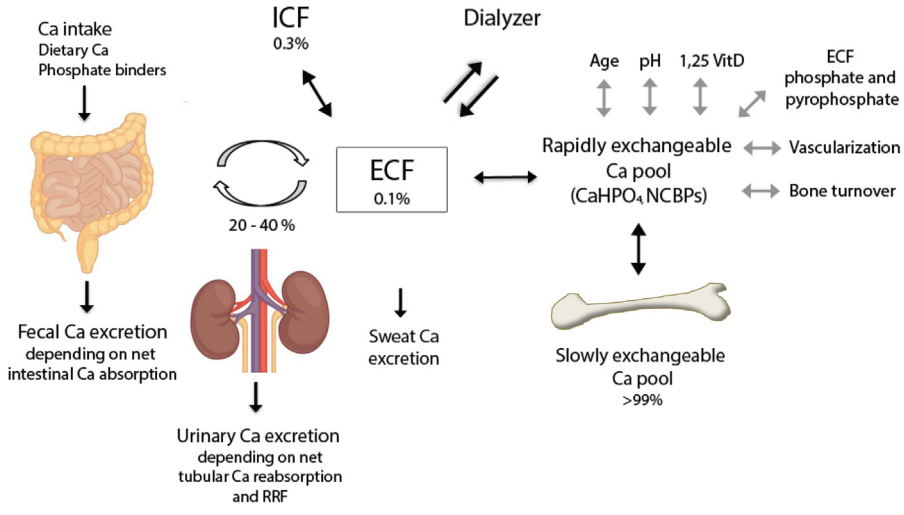

Figure 1. Calcium (Ca) homeostasis. Abbreviations: CAHPO4, brushite; ECF, extracellular fluid; ICF, intracellular fluid; NCBPs, noncollagenous bone proteins; RRF, residual renal function; VitD, vitamin D. Modified from Pirklbauer et al[16] with permission of Oxford University Press. Intestine and kidney images by Husni Bramantyo, reproduced with permission from www.1234RF.com.