Clinical application of calcium modeling in patients with chronic kidney disease

David A. Bushinsky

Department of Medicine, Division of Nephrology, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA and Department of Pharmacology and Physiology, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA

Correspondence and offprint requests to: David A. Bushinsky; E-mail: david_bushinsky@urmc.rochester.edu

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Metabolic balance studies have a long and important history in medical research [1]. On the most fundamental level balance studies are used to quantitate whether the amount of a substance (mass) has been added, retained or lost from the body. Over a fixed period of time, input and output are measured, the latter is subtracted from the former, and if there is no internal production or degradation, the results indicate either a positive (gain of mass) or a negative (loss of mass) balance. The demands of the balance technique require that the organism be in a 'steady state'; during these measurements, the ionic and hormonal milieu must be constant or, if not, at least accounted for by this now more complex model. During growth, one would expect a positive mass balance of most ions, including calcium, and with osteoporosis a negative calcium balance. However, while balance studies have value, they are not designed nor are they sufficient to understand how an ion, such as calcium, is redistributed within the body. For that more complex understanding, which can be termed kinetic modeling, one would need to know not only if the patient was in positive, neutral or negative mass balance but if an ion was moving from one body compartment to another. During growth, one would expect not only a positive mass balance for calcium but movement of this ion from the intestine into the blood and then into bone. This complex ionic choreography is controlled by a number of ions in addition to calcium and several hormones and growth factors.

With respect to calcium, as far as we know, humans do not have a mechanism to measure mass nor balance; our bodies sense only blood-ionized calcium concentration ([Ca^{2+}]), a measure of mass/volume of a liquid phase. The calcium-sensing receptor (CaR) precisely measures [Ca^{2+}] but does not detect the total calcium content nor whether it has changed [2]. While bone can respond to stress by altering its mass and architecture, calcium balance is not being detected. The clinical examples of primary hyperparathyroidism and adolescent bone growth teach us that blood calcium concentration and mass balance are not necessarily linked. Patients with primary hyperparathyroidism have an elevated [Ca^{2+}] but have a reduction in bone mineral density indicating a negative mass balance [3, 4]. In adolescents, [Ca^{2+}] is in the normal range while the growing bone incorporates calcium into the mineral, indicating a positive mass balance [5].

Humans and other mammals not only sense [Ca^{2+}] but have robust passive and active transport mechanisms to maintain it within a very narrow range [6, 7]. Altered in [Ca^{2+}] set into play physiological measures aimed at restoring the [Ca^{2+}] toward normal, with no regard to the body or bone calcium content. A low [Ca^{2+}] induces rapid physicochemical mineral dissolution—a rapidly exchangeable pool of mineral on the bone surface releases calcium in an attempt to restore [Ca^{2+}] toward normal. The low [Ca^{2+}] also induces a marked increase in parathyroid hormone (PTH) and increases the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (1,25(OH)2D). PTH stimulates cell-mediated bone resorption and renal tubular calcium reabsorption and 1,25(OH)2D increases intestinal calcium absorption and bone resorption, all resulting in increased [Ca^{2+}]. Through this process, [Ca^{2+}] is restored toward normal, often at the expense of diminished bone calcium content. The reduced calcium content weakens the bone and predisposes to fractures. In the short term, a normal [Ca^{2+}] is far more important than a normal bone mass as failure to maintain a physiologically normal [Ca^{2+}] leads to neurological dysfunction, seizures and cardiac arrhythmias and, in the extreme, death [7, 8].

With increases in dietary calcium, a decreasing percentage of that calcium is absorbed; however, absolute absorption continues to rise as intake increases [9]. In patients with intact kidney function, any absorbed calcium, in excess of body needs, is excreted in the urine. However, in patients with chronic kidney disease (CKD), the kidney does not and cannot perform this vital function [10]. Other than losses in sweat, any net absorbed intestinal calcium must be deposited either in bone or in soft tissues or lost during dialysis [11]. In patients with CKD, a number of factors induce the movement of calcium out of bone and into the extracellular fluid (ECF) [12]. Secondary
hyperparathyroidism increases both bone resorption and bone formation; however, the former predominates, adding calcium to the ECF [10, 13]. Metabolic acidosis increases physicochemical bone mineral dissolution and cell-mediated bone resorption while simultaneously decreasing bone formation [14–17], all resulting in an increase of calcium content in the ECF. Excess activated vitamin D, often given to suppress serum PTH levels, will also induce cell-mediated bone resorption [18, 19] and, again, increase ECF calcium content. Independently, each of these processes will remove calcium from bone and add it to the ECF; together, they work in concert resulting in demineralized bone and excess ECF calcium content [20]. In CKD patients on dialysis, the dialysis procedure will add or remove calcium depending on the gradient between the dialysate calcium and the [Ca^{2+}]. The ionized fraction of dialysate calcium is approximately 85–90% of the total calcium concentration of the dialysate [21]. Thus, little net calcium flux occurs in patients with a predialysis [Ca^{2+}] of 1.05–1.15 mmol/L who are dialyzed on a 1.25 mmol/L (2.5 meq/L) dialysis calcium bath. A dialysate calcium concentration of greater than ~1.25 mmol/L will favor movement of calcium into the ECF and a dialysate calcium concentration of less than ~1.25 mmol/L will favor the movement of Ca out of the ECF. Addition of activated vitamin D will also increase intestinal Ca absorption and movement of calcium into the ECF [6, 7].

The overall movement of calcium from the intestine and/or the dialysate into the ECF leads to an increase in ECF calcium content resulting in deposition of calcium in the rapidly exchangeable mineral pool on the bone surface and then into the bone mineral. Once the bone is fully mineralized or if the bone itself is the source of the calcium, the quantity added to the ECF must then increase blood calcium. However, any increase cannot continue indefinitely. Continual movement of calcium into the ECF must lead to calcium deposition in extra osseous sites. During CKD, phosphorus absorption exceeds excretion, leading to net phosphorus retention [10]. It appears that phosphorus retention results in an increase in phosphate transport into vascular smooth muscle cells, leading to upregulation of the transcription factor RUNX2, which promotes differentiation of these cells into osteoblasts [22, 23]. The newly formed osteoblasts, located in the vasculature, secrete collagen matrix. The increased ECF calcium, in the presence of retained phosphorus overwhelms inhibitors to mineralization and is deposited onto this newly formed matrix resulting in vascular calcification [22, 23].

Numerous studies demonstrate that patients with CKD have a high prevalence of vascular calcification, which is associated directly with both calcium intake and increased mortality [24–28]. Numerous other studies indicate that patients with CKD have a reduction in bone mineral content, which is associated with an increased incidence of fractures and increased mortality [29–32]. Thus, in dialysis patients, it appears that the total body calcium is redistributed, less calcium is in bone, where it should be and more is within the vascular space, were it should not be. The calcium absorbed from the diet and/or resorbed from the bone must be the source of the additional vasculature and soft tissue calcification found in CKD patients; there is no other source of this element.

I have argued previously that, in patients with CKD on dialysis, it is important to maintain a net neutral flux of calcium with respect to the ECF [12]. Determination of overall calcium mass balance is necessary but not sufficient as it does not shed light on whether calcium is moving into the ECF. Continual movement of calcium from the bone or the intestine into the ECF must result in soft tissue and/or vascular calcification, since there is no outlet for the calcium through renal excretion and the ECF calcium concentration cannot continually rise. Using available data, I have modeled net calcium movement into the ECF and determined, with a number of assumptions which are necessary because critical clinical studies on this subject have never been done, that humans on hemodialysis consuming more than ~1500 mg of elemental calcium per week without exogenous activated vitamin D and ~1000 mg of elemental calcium administered exogenous activated vitamin D will have a net movement of calcium into the ECF [12] which must ultimately result in deposition of the calcium into soft tissues, including vessels.

Some have argued for dialysis against a calcium bath of <1.25 mmol/L (2.5 meq/L) to create a negative calcium balance, which will allow for the utilization of oral calcium-based phosphate binders that create a positive calcium balance [33, 34]. The thought is to achieve an overall net neutral calcium balance over a period of time encompassing dialysis treatments. However, dialysis against a calcium bath of less than ~1.25 mmol/L results in a reduction of [Ca^{2+}] indicating that the rapidly exchangeable calcium pool in the bone cannot release calcium fast enough [35, 36]. Dialysis against a calcium bath of less than ~1.25 mmol/L is associated with an increased incidence of hypotension [35–37] and cardiovascular events, including death [38], during the dialysis period. [Ca^{2+}] is the principal regulator of PTH and the reduction of [Ca^{2+}] induced by dialysis against a calcium bath of less than ~1.25 mmol/L will stimulate PTH secretion and worsen secondary hyperparathyroidism [2, 39]. Even if overall net calcium balance is maintained by the combination of removal of calcium during dialysis treatments coupled with increased oral calcium between dialysis treatments, we still do not know whether the additional intestinal calcium from the calcium-containing binders, whose absorption is augmented by administration of activated vitamin D, is being deposited into bone or into soft tissues and vessels. A clue to the fate of this added calcium is that our dialysis patients are osteopenic and/or osteoporotic [29–32] and simultaneously have increased vascular calcium deposition [24–28].

It is not prudent to prescribe the approach of dialyzing against a calcium bath of less than ~1.25 mmol/L to remove the additional calcium absorbed from calcium-containing phosphate binders until sophisticated compartmental flux studies are done to determine the fate of the added calcium and the effects of any changes in [Ca^{2+}] on cardiovascular events and secondary hyperparathyroidism. Current kinetic calcium modeling, utilizing the inadequate available experimental data, is not sufficient to support this practice. Calcium is not a waste product, such as urea, where the only goal is sufficient removal during dialysis; calcium’s ionic concentration and compartmentalization must be rigorously maintained. Our dialysis patients are dying of cardiovascular disease [40–42], often related to vascular calcification [24–28]. We, as nephrologists, must insist that the proper


*Received for publication: 7.4.11; Accepted in revised form: 16.6.11*