

Calcium in Chronic Kidney Disease: Myths and Realities

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The kidneys, through proximal tubular active uptake or pass-through of filtered phosphorus, regulate phosphorus homeostasis in healthy individuals. Hormones and factors that contribute to the kidney regulation of phosphorus include parathyroid hormone, 1,25-dihydroxyvitamin D (1,25(OH)₂D), and fibroblast growth factor-23 (FGF-23). However, in patients with progressive chronic kidney disease (CKD), the normal homeostatic mechanisms are challenged as FGF-23 and parathyroid hormone rise and 1,25(OH)₂D levels decline. Certainly, by late stage 4 CKD and into ESRD, most of these patients exhibit frank hyperphosphatemia and have secondary hyperparathyroidism, marked elevations of FGF-23, and 1,25(OH)₂D deficiency. These changes in normal phosphate homeostasis lead in part to the manifestations of the entity known as CKD–mineral bone disorder (CKD-MBD) (1). Epidemiologic data have identified an association between the hyperphosphatemia of CKD-MBD and patient-based outcomes of vascular calcification, myocardial dysfunction, and mortality (2–5).

The management of hyperphosphatemia is currently based on a combination of three measures: dietary phosphorus restriction, dialysis, and the use of phosphate binders. The importance of phosphorus in the poor patient outcomes associated with untreated CKD-MBD is supported by the evidence that reduction of serum phosphorus, through the use of dietary phosphorus binders, improves patient survival (6–8). Our supplement, which is based on a conference held in Montreal in September 2008, focuses on some of the prevailing controversies regarding dietary phosphorus binders, leading to our symposium theme: “Myths and Realities of Calcium in CKD.”

Historically, hyperphosphatemia was first treated with aluminum-based dietary phosphate binders, for which aluminum hydroxide was widely used. Because severe toxicity of aluminum overload was noted in patients with ESRD, calcium-containing dietary phosphorus binders have been used preferentially for over the past 25 yr. More recently, concerns regarding the use of calcium-based dietary phosphorus binders (which are discussed extensively in this supplement) have led to the use of other agents, including polymers, salts, rare earth metals, and newer compounds in development.

However, calcium salts are still used worldwide, and their

advantages and disadvantages remain controversial and open for discussion. For example, concern over dietary calcium, either as a supplement in older women with osteoporosis or as a dietary phosphorus binder in patients with CKD and ESRD, may accelerate arterial vascular calcification (including the coronary bed) with ensuing deleterious cardiac consequences (9–12).

At the same time, calcium is a critical and necessary component because of its key roles in a wide range of biologic functions, including skeletal mineralization, a subject itself of great importance in CKD-MBD. The body's calcium requirements are not fixed but vary according to developmental status from the fetus, into childhood and adolescence, and through several stages of adulthood, including pregnancy. Thus, the potential advantages and risks of high or low levels of dietary calcium supplementation need to be analyzed in context and often individualized. It is known that calcium supplementation can correct a negative calcium balance in the growing child, in some postmenopausal women, and in some elderly individuals who may be in very negative calcium balance. In such individuals (generally when the subject also has vitamin D sufficiency), calcium can help to prevent bone loss and may have a beneficial effect for promotion of bone mass. The effect of calcium alone on bone fractures appears to be absent, unless combined with the administration of vitamin D. However, these unique examples are not what we believe to be true for most individuals. In individuals in whom the calcium balance is not negative or, more commonly, is neutral or positive, calcium may negatively affect bone and vessels. Examples of this positive balance include patients with CKD, ESRD, perhaps most women with postmenopausal osteoporosis, and the elderly in general.

It is important to understand that the renal capacity of handling calcium varies in the different stages of CKD. From at least CKD stage 3 and onwards, calcium excretion in the kidney is diminished rather than enhanced, as is often believed. A positive calcium balance arises easily because the intestinal absorption of calcium is greater than the kidney's capacity for its excretion. This is particularly important if nephrologists omit dietary calcium (including supplements) in their assessment of the total calcium dosage received by patients with CKD and ESRD, where calcium-based dietary phosphorus binders are often prescribed. It is important to emphasize that calcium from the phosphorus binder is absorbed and needs to be

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considered when calculating the total calcium intake in the patient with CKD.

In healthy individuals, the recommended dietary allowance for calcium is approximately 1 g/d (13), which seems to be sufficient to prevent a negative calcium balance under most circumstances. However, in CKD the precise dose has not been accurately determined. If we assume that we can use the figure adopted for the general population and apply it to the calcium-based dietary phosphorus binder, where a dose of 1g is not uncommonly used, then a patient with CKD should not receive any additional calcium so as to avoid a positive calcium balance. This aspect is even more important in patients with ESRD, where calcium balance is affected by influx or efflux from the dialysate. Although several countries have adopted a 2.5-mEq/L calcium concentration in the dialysis fluid, a concentration that itself does not promote calcium influx, a great number of countries still routinely use 3 or 3.5 mEq/L of calcium in the dialysis fluid, which will result in a positive calcium influx.

What are the reasons calcium supplementation is used in CKD stages 3 to 5? It is often said that patients are treated with calcium for hypocalcemia. Hypocalcemia is quite uncommon in CKD stage 3 and early stage 4, but more often observed in stage 5. For patients with early stage CKD, the routine use of calcium in the form of supplements or as a binder salts is not indicated. On the contrary, such calcium usage may increase the risk of undesirable and detrimental effects resulting from a positive calcium balance. It is more important to pay attention to, and correct, nutritional vitamin D deficiency in patients with CKD stages 3 or 4. This correction will lead to better protection against hypocalcemia and may reduce secondary hyperparathyroidism while avoiding the risk of a calcium load. Even in patients in CKD stage 5 with hypocalcemia, there is some discussion of whether oral calcium salts are the optimal means of treating this finding.

Apart from the attention given to the overall state of calcium balance in the patient with CKD, there is a need to avoid positive calcium balance in those patients who manifest or are at greater risk of vascular calcification. In this group, we also should consider the youngest patients because, in addition to the well-known risk groups such as those with diabetes mellitus or hypertension, pediatric subjects may also have pathologic vessel calcium accumulation (14). Although we need more studies to address these issues, it seems reasonable and good clinical practice to avoid any possibility of calcium load in these groups of patients with CKD, to minimize risks to their general health status and survival.

In summary, despite the great importance of calcium in health, development, and growth, its administration may not always be “healthy.” Calcium should be regarded as a therapeutic agent in CKD and, as in all other such therapies, it requires a careful analysis of risks and benefits before being recommended and prescribed. The following articles present the many “myths and realities” about calcium as a supplement and as a dietary phosphorus binder that merit further discussion. We are confident that our readership will find the articles in this supplement a great help to a better understanding of the advantages and disadvantages of calcium use in CKD.

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