How well do we understand calcium and vitamin D?

Vitamins and supplements are a huge part of the health and wellness scene, and increasingly a part of mainstream medical care as well. Patients and the "healthy well" are pursuing alternative, complementary, and integrative approaches. Patients and physicians are looking for solutions to problems that are not being solved through more traditional paths, or they have an aversion to the side effects of prescription drugs. I understand the reasoning, and I have discussions almost daily about there being no free lunch with medications that short-circuit human physiology. The drug that has zero side effects is not likely a drug. We discuss that "natural" does not mean "safe." Then we discuss the value and limitations of using evidence from well-designed clinical trials to inform our treatment decisions. And perhaps most important, if relevant, we discuss the side effects of *not* treating an underlying disease for which there are effective therapies.

With so much emphasis on clinical trials, evidence-based joint decision-making, and comparative-benefit studies when choosing treatment, the growth of the supplement market is a strong comment on the perceived and often real failings of traditional therapies. It also reflects our apparent failure as a profession to educate ourselves and the public about the difference between anecdote-based belief and clinical trial-based confidence, the difference between evidence and innuendo, and, equally important, the limitations of applying population-based clinical trial data to an individual patient.

Which brings me to the discussion of calcium and vitamin D supplementation by Drs. Kilim and Rosen in this issue of the *Journal* (page 543). We know a lot about calcium homeostasis and the role vitamin D plays in regulating circulating calcium levels. Only a small fraction of the calcium in the body circulates (most is in our skeleton), and likely only about 1% is truly exchangeable. But the circulating free calcium level is tightly controlled, as the function of our neuromuscular system, brain, and heart depend on keeping intra- and extracellular calcium levels within precise limits. If necessary, our bodies maintain stable levels of circulating free calcium at the expense of leaching calcium from our bones, placing us at risk of potentially fatal fractures. Thus was born the concept of guaranteeing adequate calcium stores through calcium supplementation.

Control of the free calcium level is not simple. There are several interrelated sensing and modulatory pathways, eg:

- Gut absorption, which is affected by the total gut load of calcium, intestinal integrity, and the specific ingested foodstuffs, and likely by our microbiome
- The parathyroid hormone (PTH) level, which directly or indirectly affects calcium absorption, the calcium-phosphate ratio, and thus, extraskeletal calcium localization and bone calcium content
- Vitamin D, with its many effects after interorgan multistep activation.

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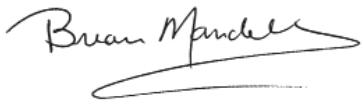
Despite this knowledge of calcium metabolism and the intricate cross-talk between the different pathways, I do not believe we truly understand how to determine the amount of dietary and supplemental calcium or vitamin D that is ideal for a given patient. I also do not believe we know with certainty what is the "normal" or ideal 25-hydroxyvitamin D level in that same patient: note the different ranges of normal proposed by different expert working groups.

How do we know when there is insufficient calcium in our diet? The total or free circulating calcium level is far too insensitive and, as noted above, complex homeostatic mechanisms are always trying to maintain an appropriate physiologic calcium level, whatever the intake. Urinary calcium excretion does not necessarily equal the ingested calcium load; there are too many factors influencing renal calcium excretion. Gastrointestinal excretion is also variable and complex. We know when the vitamin D level is functionally much too low, as the PTH level begins to rise; but the "normal" PTH range is wide, and the slope of the relationship between vitamin D and PTH is affected by many factors.

Additionally, accumulating information suggests that vitamin D metabolites significantly affect immune regulation and the onset and expression of a number of organ-specific and systemic autoimmune disorders. Further, the ideal 25-hydroxyvitamin D level for a healthy immune system is not known. Does the body have to compromise something in reconciling the target for a healthy skeleton and the target for a healthy immune system, which may conceivably be different? But importantly, this new knowledge does *not* imply that vitamin D supplementation will reduce the pain and symptoms from inflammatory arthritis or noninflammatory fibromyalgia.

Despite these many areas of uncertainty, Kilim and Rosen focus on bone health, summarize the wealth of accumulated data, and provide practical management advice we can use in the clinic. But if we struggle so much to know the correct way to manage calcium and vitamin D supplementation in our patients, it is little surprise that most of us struggle even more when asked about using supplements for which the biology is far less understood. As a medical community, we need to uniformly address this lack of understanding wherever it exists. Believing in a supplement or a treatment is not the same as understanding it or having strong evidence about its efficacy and safety.



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