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In the current era of rapid dissemination of medical information, it is paradoxically difficult sometimes for patients to make the appropriate choices regarding their health. As part of their training and culture, physicians generally examine the results of a given study in the context of an overall body of evidence. By contrast, patients are often perplexed by the results of a given, possibly well-publicized study (or set of studies) that may be at odds with the advice their own physician has provided them. Potential outcomes of this include a change in behavior or medications by the patient or, hopefully, an extended discussion with their physician regarding the appropriate course of action.

A case in point is the previously simple issue of calcium and vitamin D supplementation as part of an overall regimen for the prevention or treatment of osteoporosis. This was highlighted to me by a recent patient with osteoporosis who returned for a follow-up visit. Per my usual practice, I had asked her to take approximately 800 IU of vitamin D and 1200 mg of calcium and she had followed this advice for many years. On this occasion, however, as I went through her list of medications, I discovered that through various supplements, she was consuming approximately 6000 IU of vitamin D and had discontinued all calcium supplements. When I pressed her for her reasons for these changes, she replied that all of her reading indicated that "vitamin D was good for you and prevented fractures, cancer, and heart disease, whereas calcium supplements caused heart attacks." As I considered how best to respond (my initial reaction was a sense of exasperation), I came to realize that from her perspective, she was just trying to be an educated, responsible patient. Other than the fact that she should have checked with me before changing her regimen, she was simply reacting to information she (and other patients like her) are being flooded with regarding osteoporosis and a host of other medical issues.

It is in this context that the 2010 Institute of Medicine (IOM) report on dietary reference intakes for vitamin D and calcium is of particular importance (1). The key findings of this report are nicely summarized by the members of the IOM Committee in this issue of *JCEM* (2) and serve to bring clarity, for physicians and patients, on the overall body of evidence on which to base recommendations for vitamin D and calcium supplements.

As reflected by the decisions made by the patient described above, there has been considerable interest and publicity on the potential benefits of vitamin D supplementation in not only preventing fractures, but also reducing the risk of cardiovascular disease, diabetes mellitus, cancer, and immune dysfunction (3). To rigorously evaluate the evidence for each of these outcomes, the IOM Committee used two key systematic reviews conducted by the Agency for Healthcare Research (AHRQ) in 2007 (4) and 2009 (5), and also conducted its own literature review. A variety of specific skeletal and nonskeletal "indicators" on which to base the current recommendations were used.

As summarized by Ross *et al.* (2), the IOM Committee concluded that bone health was the only outcome for which the available evidence was sufficient to support the development of a dietary reference intake (DRI) for calcium and vitamin D. The development of the DRI also includes specification of the estimated average requirement (EAR; corresponding to the median intake of the population), the recommended dietary allowance (RDA;

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Abbreviations: CI, Confidence interval; DRI, dietary reference intake; 25OHD, 25-hydroxyvitamin D; RDA, recommended dietary allowance; UL, upper intake level.

corresponding to the level of intake that would meet the requirements of at least 97.5% of the population), and the tolerable upper intake level (UL; corresponding to the highest daily intake of the nutrient that is likely to pose no risk). The major conclusion and message for patients and physicians is that for optimal skeletal health, the RDA for calcium for women and men between the ages of 19 to 50 yr is 1000 mg/d, stays at 1000 mg/d for men aged 51–70 yr, but increases to 1200 mg/d for women aged 51–70 yr and for women and men aged 71 yr and older. The RDA for vitamin D is now set at 600 IU/d for all individuals between the ages of 1 and 70 yr, increasing to 800 IU/d for those 71 yr and older. In general, this level of vitamin D intake would ensure serum 25-hydroxyvitamin D (25OHD) levels of 20 ng/ml or higher in virtually all individuals. Along these lines, the IOM Committee felt that there was insufficient evidence to use a target serum 25OHD level of 30 ng/ml or higher, as has been recently suggested by some experts (3). The Committee also set tolerable ULs of 2000 mg/d for calcium and 4000 IU/d for vitamin D. These guidelines should provide a very useful framework for counseling our patients; however, there are several implications of these recommendations and areas where patients are likely to have further questions that are worth highlighting.

First, patients are likely to ask how much of an effect calcium and vitamin D supplementation, as recommended above, is likely to have on reducing the risk of fracture. Perhaps the best estimates of this come from several meta-analyses (6, 7); for example, Tang *et al.* (7) combined results from 17 trials (n = 52,625) that reported fracture as an outcome and found that calcium and vitamin D supplementation was associated with a 12% risk reduction in all fractures [risk ratio, 0.88; 95% confidence interval (CI), 0.83–0.75]. In trials that reported bone mineral density as an outcome (23 trials, n = 41,419), calcium and vitamin D treatment was associated with reduced rates of bone loss (relative to placebo) at the hip of 0.54% (95% CI, 0.35–0.73) and spine of 1.19% (95% CI, 0.76–1.61). To put this in context for patients, the commonly used drug for osteoporosis, oral alendronate, reduces hip fracture risk by 51% and increases hip and spine bone mineral density over 3 yr by 4.7 and 6.1%, respectively, compared with placebo (8). Thus, whereas calcium and vitamin D do have beneficial effects on fracture risk and rates of bone loss, the magnitude of this effect is much smaller than that of standard pharmacological therapy. However, given the low cost and minimal side effects of calcium and vitamin D supplementation, this should be part of the regimen for the prevention or treatment of osteoporosis in virtually all patients (unless there are specific contraindications, such as a history of nephrolithiasis or known hypercalciuria).

As exemplified by my patient above, patients may also wonder about the attention given in recent years to possible effects of vitamin D in reducing the risk of cancer, cardiovascular disease, diabetes, infections, autoimmune disease, and other extraskeletal outcomes. However, as noted by Ross *et al.* (2), the IOM Committee concluded that there was insufficient evidence, particularly from randomized trials, that vitamin D treatment affected the risk of these nonskeletal outcomes. Thus, whereas observational studies have demonstrated associations between low 25OHD levels (below 20 ng/ml) and increased risk of several nonskeletal outcomes (summarized in Ref. 3), these findings could be confounded by a number of factors— one hardly needs to be reminded of the disparate findings with regard to the relationship of estrogen therapy and cardiovascular disease from observational studies *vs.* the interventional data from the Women's Health Initiative (9). The IOM Committee also noted with some concern that recent observational evidence raises the issue of whether there is a curvilinear or U-shaped curve for some outcome measures, including cardiovascular disease, vascular calcifications, pancreatic cancer, and mortality (2). These studies suggest that the lowest risk for these adverse outcomes may occur at intermediate 25OHD levels, with risk increasing at both low and high levels. The uncertainties in this area were recently highlighted by a randomized controlled trial of high-dose vitamin D (a single annual dose of 500,000 IU or placebo) in elderly community-dwelling women (10). Surprisingly, the women receiving high-dose vitamin D had an increased risk of falls (by 15%) and fractures (by 26%). Although the underlying biological basis for these findings remains unclear, based on the combination of observational data and this interventional study, the IOM Committee did recommend a tolerable UL for vitamin D intake of 4000 IU/d (2).

A third question that patients, such as the one described above, have begun to ask me is whether calcium supplements lead to an increased risk of myocardial infarction? This is an issue with the IOM recommendations, which provide an RDA of 1000–1200 mg/d of calcium for individuals over the age of 50 yr. The basis for the concern regarding calcium supplementation and myocardial infarction comes from a metaanalysis by Bolland *et al.* (11) that evaluated 11 randomized controlled trials of calcium supplements (without coadministered vitamin D) and concluded that calcium supplementation (≥500 mg/d) was associated with an approximately 30% increase in the risk of myocardial infarction. Although this analysis does raise concerns about the safety of calcium supplements, several caveats need to be kept in mind. First, this meta-analysis only pertains to studies using calcium alone (with-

out vitamin D), which is different from the IOM recommendations and current practice. Second, the individual studies included in the metaanalysis did not necessarily adjudicate or validate cardiovascular events, leading to potential misclassification. Third, using strict validation criteria for cardiovascular endpoints, Lewis *et al.* (12) recently reported results of a 5-yr randomized controlled trial of calcium carbonate (without supplemental vitamin D) and 4.5 yr of posttrial follow-up. In this study, 1460 women (mean age, 75 yr), were randomized to receive 1200 mg of calcium carbonate daily or placebo, and the intervention group that received calcium supplementation did not have a higher risk of death or first-time hospitalization from atherosclerotic vascular disease (multivariate-adjusted hazard ratio, 0.938; 95% CI, 0.727–1.146). Nonetheless, in advising patients, it is important to stress that excessive calcium intake could have adverse side effects, including nephrolithiasis and perhaps unknown cardiovascular effects. As such, patients should aim for a total calcium intake (diet plus supplements) of 1000–1200 mg/d (based on the age and gender guidelines in the IOM report). For example, if a patient already consumes two glasses of milk per day, they would only need a single 600 mg supplement to achieve the target daily intake of 1200 mg. It is important to review this issue with patients because some may assume that they need to take 1200 mg daily of supplements in addition to what they may be consuming in their diet, leading to possibly excessive levels of calcium intake (*i.e.* above the tolerable UL of 2000 mg/d recommended by the IOM Committee).

In summary, the case of calcium and vitamin D supplementation is a good example of patients struggling, at times, to chart the appropriate course for their health in the face of potentially conflicting information from their physicians *vs.* through various forms of media, especially with regard to the results of specific, high-profile studies. This is where expert groups, such as the IOM Committee, can bring clarity to these issues for patients as well as physicians. Not everyone may agree with the IOM report; however, my reading of the report and the summary presented by Ross *et al.* (2) is that the panel acted responsibly in reviewing the overall body of evidence and carefully following the time-honored dictum of "*primum non nocere.*"

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References

1. **Institute of Medicine** 2010 Dietary reference intakes for calcium and vitamin D. Washington DC: The National Academies Press
2. **Ross C, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Ramon A. Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, Kovacs CS, Mayne ST, Rosen CJ, Shapses SA** 2011 The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab 96:53–58
3. **Holick MF** 2007 Vitamin D deficiency. N Engl J Med 357:266–281
4. **Cranney A, Horsley T, O'Donnell S, Weiler HA, Puil L, Ooi DS, Atkinson SA, Ward LM, Moher D, Hanley DA, Fang M, Yazdi F, Garritty C, Sampson M, Barrowman N, Tsertsvadze A, Mamaladze V** 2007 Effectiveness and safety of vitamin D in relation to bone health. Evid Rep Technol Assess 158:1–235
5. **Chung M, Balk EM, Brendel M, Ip S, Lau J, Lee J, Lichtenstein A, Patel K, Raman G, Tatsioni A, Terasawa T, Trikalinos TA** 2009 Vitamin D and calcium: a systematic review of health outcomes. Evidence report no. 183. (Prepared by the Tufts Evidence-based Practice Center.) AHRQ Publication no. 09-E015. Rockville, MD: Agency for Healthcare Research and Quality
6. **Avenell A, Gillespie WJ, Gillespie LD, O'Connell D** 2009 Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst Rev 2:CD000227
7. **Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A** 2007 Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet 370:657–666
8. **Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE** 1996 Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet 348:1535–1541
9. **Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J** 2002 Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 288:321–333
10. **Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D, Nicholson GC** 2010 Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA 303:1815–1822
11. **Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, Reid IR** 2010 Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ 341:c3691
12. **Lewis JR, Calver J, Zhu K, Flicker L, Prince RL** 7 July 2010 Calcium supplementation and the risks of atherosclerotic vascular disease in older women: results of a 5-year RCT and a 4.5-year follow-up. J Bone Miner Res doi: 10.1002/jbmr.176