



UPDATE OF VITAMIN D

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As readers of this *Journal* may recall, the Winter 2006-07 issue of *JLGH* (Volume 1, No. 3) was devoted to a comprehensive review of Vitamin D. Since that time there have been multiple articles concerning this subject in the medical and lay presses, including a 1,000 page report (with Appendices) from the Institute of Medicine (IOM) with their latest recommendations.

For those 71 years of age and older, the IOM increased the recommended daily allowances (RDA) from 600 International Units (IU) daily to 800 IU. For everyone under 71 years (including children) the RDA increased to 600 IU, with the only exception being infants under one year of age, for whom an "adequate intake (AI) is 400 IU. (RDA's have not been established for infants.) The dietary reference intake process also specifies the tolerable upper intake level (UL = the highest daily intake of the nutrient that is likely to pose no risk). That limit was increased to 4000 IU daily from nine years of age onward.

The dietary reference intakes are developed for "normal healthy persons" in the North American population. They are not intended for individuals with specific disease states, and are provided separately for groups in several age and gender life-stages.^{1,2}

The RDAs for vitamin D were increased because randomized controlled trials (RCTs) supported a key cause-and-effect role for calcium and vitamin D in skeletal health. Notably, however, the evidence for extraskeletal benefit from Vitamin D, including cancer, cardiovascular disease (CVD), diabetes, and autoimmune disorders, was inconclusive as to causality, and insufficient to inform nutritional requirements. Therefore, the recommendations are based on bone health, and the new RDAs cover the requirements of 97.5% of the population. The recommended serum 25-hydroxy vitamin D [25(OH)D] level is at least 20 ng/mL (50 nmol/liter). The Committee concluded that the prevalence of vitamin D inadequacy in North America has been overestimated. They cited areas in which urgent research and clinical priorities are needed to avoid both undertreatment and overtreatment.

As has been cited in *JLGH* previously in our articles, there have been many longitudinal and case controlled studies involving vitamin D, but few RCTs that demonstrate cause and effect. A review of the different levels of evidence can be done according to the following hierarchy: meta-analyses of randomized controlled trials (RCTs), individual RCTs, nonrandomized intervention studies, meta-analyses of observational cohort and case-controlled studies, and individual observational studies.³ For example, one of the limitations of a cross-sectional study like NHANES (National Health and Nutrition Examination Survey) is that it can demonstrate only associations, not cause-and-effect relationships. For example, though people with significant disease may be found to go outside less often to accumulate the sun's rays, one cannot infer that their low vitamin D level causes their chronic disease in any manner.

I would like to point out though that although the IOM states that their new higher RDAs meet the requirements of the majority of the normal population, physicians are generally caring for many who don't meet those "normal" requirements. Moreover, the IOM states that potential biases must be carefully considered in the interpretation of all observational studies. In this regard, it was noted that many micronutrients (such as B-carotene, vitamins C and E, folic acid, and selenium) that initially seemed promising in observational studies, did not withstand rigorous testing and clinical trials, and may even sometimes be hazardous with high levels of supplementation.

VITAMIN D AND BONE HEALTH

Let's look at some of the data that the IOM reviewed, as well as some articles that have been published since then. While the IOM recommendation of an increase in vitamin D intake is supported by the available data from double-blind RCTs of fracture risks, the threshold of 20 ng/mL for its 25(OH)D blood level is not. In two 2009 meta-analyses of double-blind RCTs, a threshold of 20 ng/mL was insufficient to reduce

fractures or falls based on achieved 25(OH)D levels in the treatment groups.^{4,5} Also, in the very large population-based NHANES analysis, bone density in both younger and older adults increased with increasing 25(OH)D levels far beyond 20 ng/mL, which suggests that the recommended IOM threshold is too low for optimal bone health in adults. In contrast to the IOM report, the International Osteoporosis Foundation (IOF), in their 2010 position paper on vitamin D, recommended a threshold of 30 ng/mL for optimal fall and fracture reduction and recommended 800 to 1000 IU of vitamin D per day for seniors aged 60 years and older.⁶ An added comment from Drs Bischoff-Ferrari and Willett states “the IOM conclusion that intakes of vitamin D are adequate for most of the US population assumes that lack of randomized trials means lack of benefit, which seems illogical.”

VITAMIN D AND CARDIOVASCULAR DISEASE (CVD)

There are two randomized trials that looked at CVD event rates with supplementation of vitamin D versus placebo. In a trial in the United Kingdom, which randomly assigned 2037 men and 649 women to receive 100,000 IU of oral vitamin D or placebo every four months, the risk for total CVD (RR, 0.90), CVD mortality (RR, 0.84), and non-fatal CHD (RR, 0.94), were all slightly lower in the vitamin D group, but the differences were statistically insignificant.⁷ The cardiovascular endpoints were not primary endpoints.

A more recent randomized trial of 302 elderly women in Australia investigated the effect of calcium supplements, 1000 mg day plus vitamin D, 1000 IU/day, compared with calcium supplements plus a placebo instead of vitamin D. The group that received both calcium and vitamin D had lower rates of ischemic heart disease (1.3% versus 2.0%) but similar rates of stroke (2.0% for both).⁸ Again the primary endpoint of this study was the incidence of falls; the incidence of CVD events was secondary.

Two other randomized trials of vitamin D supplementation reported CVD event rates. Those two trials tested combined supplementation of vitamin D and calcium versus double placebos, and both trials showed no difference in the risk of cardiovascular events between treatment groups.^{9,10} Notably, the vitamin D dosage of 400 IU per day used in the women's health initiative increased the plasma 25(OH)D levels to less than 30 ng/mL.

Only one prospective study examined use of vitamin D supplements and risk for CVD events in the

general population and found a very small benefit. This study assessed nutrient intake with validated questionnaires, but did not adequately evaluate participants' sun exposure and duration of supplement use. Among 34,486 postmenopausal women without baseline CHD, the age-adjusted relative risk (RR) of CHD mortality for those who consumed Vitamin D < 400 IU/d was .81, and for those who took > 400 IU/d it was 0.80 (CI, 0.63 to 1.03) compared with nonrecipients. Adjustment for other potential confounders attenuated the corresponding RRs to 0.86 and 0.85, respectively.¹¹

In patients with congestive heart failure, we do know that vitamin D supplementation improves cytokine profiles as shown in a double-blind, randomized, placebo-controlled trial.¹² In this study parathyroid hormone was significantly lower and anti-inflammatory cytokine interleukin 10 was significantly higher in the group supplemented with Vit. D after nine months. Survival rate, however, did not significantly differ between the study groups during a 15 month follow up.

There may be other cardiovascular reasons that vitamin D supplementation may be helpful. In a study of 82 vitamin D-deficient myalgic patients taking statins, 38 were given vitamin D at 50,000 units per week for twelve weeks while continuing statins, with a resulting increase in serum vitamin D from 20.4 to 48.2 ng/mL ($P < 0.0001$) and resolution of myalgia in 92% of the patients.¹³

Concerning hypertension, 11 RCTs fulfilled inclusion criteria to compare blood pressure levels in those receiving vitamin D or placebo. An insignificant reduction in systolic blood pressure was found, but there was a small, statistically significant reduction in diastolic pressure. In those who were normotensive at baseline, there was no reduction in blood pressure.¹⁴

VITAMIN D AND RENAL DISEASE

Patients with renal disease commonly have vitamin D deficiency and receive treatment with active vitamin D. At least five identified studies that examined the association between active use of vitamin D and CVD mortality in patients on dialysis showed significantly less CVD mortality with Vitamin D supplementation.¹⁵ Another recent article found that paricalcitol reduced albuminuria in patients with type II diabetes (VITAL study). The addition of 2 µg per day safely lowered the residual albuminuria in patients with diabetic nephropathy, and therefore could be a novel approach to lower residual renal risk in diabetes.¹⁶

There have been suggestions that vitamin D supplementation is a risk factor for nephrolithiasis and hypercalciuria, but there have been no RCTs reported in which the effects of standard replacement doses of vitamin D have shown increased lithogenicity. Given that hypercalciuria is associated with increased rates of bone loss among patients with recurring kidney stones, vitamin D sufficiency is likely of particular importance in this patient population.¹⁷ Dr. David Leaf in a recent Letter to the Editor in *The New England Journal of Medicine* stated “until additional data are available, I would suggest that vitamin D therapy, if indicated, should not be withheld from patients with recurrent kidney stones, even in the presence of hypercalciuria.”

There were suggestions in the IOM Report that excessive amounts of vitamin D might increase the possibility of pancreatic or prostate cancer. Unfortunately the published studies again are not RTCs. A prospective, nested case-control study of vitamin D status and risk of pancreatic cancer in male smokers showed higher vitamin D concentrations were associated with a three-fold increased risk for pancreatic cancer.¹⁸ However, another study did not confirm the association between 25 (OH)D and pancreatic cancer in a nested case-control study in the Prostate, Lung, Colorectal, and Ovarian screening trial.¹⁹

Both high (>80 nmol/L) and low (<19 nmol/L) levels of blood of 25(OH)D were found to be associated with a higher prostate cancer risk in a longitudinal, nested case-control study in the Nordic countries. It was recommended that vitamin D deficiency be supplemented, but excessive vitamin D might also enhance cancer development.

WHAT IS THE PRESENT BOTTOM LINE CONCERNING VITAMIN D SUPPLEMENTATION?

We all take care of patients with different health issues. My patient population, for example, is primarily geriatric with an epidemic of osteopenia and osteoporosis. The randomized controlled studies are clear that in this population vitamin D supplementation is advantageous. For those of you who care for primarily healthy middle aged patients, the IOM recommendations, with the inclusion of the increased RDA recommendations for vitamin D, are most likely adequate. There is no question that more randomized controlled studies are needed. There is an ongoing vitamin D and omega-3 trial (VITAL: Clinical Trials.

gov # NCT01169259). This is a five year randomized placebo-controlled trial of 20,000 US males and females examining vitamin D supplementation of 2000 IU per day with or without supplementation with n-3 fatty acids for primary prevention of cancer and cardiovascular disease. Lancaster General Health is considering being a site for this trial. If this comes to fruition, I will certainly let you know. It would be undertaken through The Heart Group of Lancaster General Health.

Vitamin D and calcium are independently and interactively involved in many molecular pathophysiological processes related to the development of cardiovascular disease. Vitamin D down-regulates the renin-angiotensin system, improves insulin secretion and sensitivity, inhibits vascular smooth muscle cell proliferation, protects normal endothelial cell function, and modulates inflammatory processes. Epidemiologic studies have found an association between vitamin D insufficiency, reflected by low serum 25(OH)D levels, and higher rates of CVD morbidity and mortality. High calcium intake promotes the influx of calcium into cells. Optimal intracellular calcium levels, also homeostatically controlled by active vitamin D and parathyroid hormone, inhibit fatty acid synthesis and activate lipolysis in adipocytes, improve insulin secretion from pancreatic B cells, enhance insulin sensitivity in peripheral organs, suppress platelet aggregation, attenuate vascular smooth muscle tone, and augment vasorelaxation. Despite all these known processes, we still need randomized placebo-controlled studies to prove cause and effect with improved outcomes.

The IOM report states that we should keep our 25(OH)D levels below 50 ng/L, as potential risks may increase above that level. In addition to those who need it for bone health, the studies I quoted above show that vitamin D supplementation consistently improved mortality in dialysis patients. There is also a randomized controlled double blind study reported in the *American Journal of Clinical Nutrition* in May 2010, showing that 1200 units of vitamin D (versus placebo) decreased influenza by 42% in school children. In doing so, it also decreased asthma attacks to only 2 children in the vitamin D supplemented group versus 12 in the non-supplemented group.

The whole question of who needs to be tested for vitamin D deficiency, who needs to be treated, and how much vitamin D supplementation should be

used, will have to await further RCTs. In the meantime, we know that older, sicker adults are more likely to have inadequate vitamin D levels. A recent article in the Mayo Clinic Proceedings suggested the following groups might be tested:²⁰

- Dark skin;
- Osteoporosis or previous skeletal fracture;
- Certain laboratory abnormalities (low urine calcium, low serum calcium, low serum phosphorus, elevated alkaline phosphatase, elevated parathyroid hormone);
- Chronic kidney disease, renal insufficiency, or nephrotic syndrome;
- Chronic musculoskeletal pain or weakness;
- Malnutrition/poor oral intake;
- Malabsorption syndromes, celiac disease, inflammatory bowel disease;
- Liver disease, liver failure.

In addition, certain antiepileptic medications can increase metabolism of vitamin D. Other medications reduce the absorption or interfere with the metabolism of vitamin D, including cholestyramine, cholestipol, orlistat, mineral oil, and ketoconazole.

Vitamin D is stored in adipose tissue and therefore, may have reduced bioavailability in obese individuals, who could have lower serum levels and require higher intake to achieve comparable levels. Weight reduction studies show that serum vitamin D levels increase as individuals lose weight.

Finally, a possible potential for conflicts of interest among the IOM committee members was initially brought up jointly by Dr. John J. Cannell and the Vitamin D Council, and The Alliance for Natural Health. They contend that the IOM committee solicited but then suppressed commentary on the new vitamin D and calcium recommendations from 14 nationally recognized nutrition experts, including Professor Robert Heaney at Creighton University, and Dr. Walter Willett at Harvard University. The Vitamin D Council and the Alliance for Natural Health are calling on the IOM to release these 14 comments under The Freedom of Information Act. The fact that at least two of the committee members have direct ties to drug companies developing analogs of vitamin D does not prove bias, nor does it necessarily invalidate the IOM's report. These groups, however, are raising legitimate concerns about potential conflict of interest and the omission of potentially important dissenting opinions.

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