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EDITORIAL

Vitamin D and fat: the chicken versus the egg

Vitamin D is literally the "hot" vitamin of the day. The last few years have been notable for increased clinical interest and research in how this vitamin impacts health outside its known benefits with respect to bone and mineral metabolism. Specifically, vitamin D deficiency has been linked to increased risk of certain autoimmune diseases (eg, type 1 diabetes mellitus and multiple sclerosis), cancers (eg, colon, prostate, and breast), infections (eg, *Mycobacterium tuberculosis*), cardiovascular diseases (eg, hypertension and type 2 diabetes mellitus), and psychiatric illnesses (eg, depression and schizophrenia).[1,2] Low vitamin D has even been associated with increased risk of death, though causality has not been established.[3] Serum 25-hydroxyvitamin D (25OHD) levels are determined by the dietary intake of vitamin D and the synthesis of vitamin D by ultraviolet light in the skin.[4] Serum levels of 25OHD reflect total body stores of vitamin D and are used to define vitamin D deficiency, whereas 1,25-dihydroxyvitamin D that is formed in the kidney is the metabolically active form of vitamin D.[5] Determining the 25OHD level at which an individual is "deficient" is made much more challenging because of problems inherent in the 25OHD assays and epidemiologic data suggesting that different endpoints have differing optimal 25OHD levels.[6,7] Notwithstanding these issues, there is great interest in determining how vitamin D impacts health, and a sense that in the near future, the recommended daily allowance of vitamin D will be increased to achieve higher serum 25OHD levels.

In this issue of *Menopause*, Moschonis et al[8] add to our understanding of how low 25OHD levels may impact health through their assessment of the relationship between body composition and 25OHD levels. The investigators meticulously studied 112 postmenopausal nonosteoporotic women, aged approximately 60 years old with body mass index of approximately 30 kg/m^2, from the Postmenopausal Health Study that was conducted in Greece. The 25OHD level was assessed on a single blood sample by chemiluminescence assay, and levels ranged from 10 to 46 ng/mL. Expectedly, parathyroid hormone levels were significantly lower in the women with the highest 25OHD levels (measured in tertiles). Notably, the women did not consume much vitamin D in their diets, with mean (±SD) daily dietary intake of 24 (±32) international units. The participants differed, however, in their exposure to sunlight, with the UV-B exposure in the women with the highest 25OHD levels being almost twice that of the other women. Although there was no difference in strength or anthropometric indices based on 25OHD tertile, body composition differed significantly, even after Bonferroni correction for multiple analyses. Specifically, women in the lowest 25OHD tertile had significantly more extremity fat mass than that of women in the highest tertile. These findings are consistent with those from other cohorts of men and premenopausal and postmenopausal women.[9,10] Conversely, women in the highest 25OHD tertile had quantitatively more fat-free mass than that of women in the lowest 25OHD tertile; however, not all endpoints met statistical significance. In addition, insulin growth factor 1 (IGF-1) levels were significantly higher in the women with the highest 25OHD levels, though on bivariate analysis, the relationship between 25OHD and IGF-1 did not meet statistical significance. With multivariable regression analysis, after controlling for UV-B exposure, parathyroid hormone, IGF-1, and physical activity, fat mass was still negatively associated with 25OHD levels and fat-free mass positively associated with 25OHD levels.

With regard to the physiology to explain these findings, the authors provide a number of explanations. They appropriately discuss the fact that the negative association between 25OHD levels and fat mass may be secondary to the increased sequestration of vitamin D in fat. Indeed, they speculate that body composition might need to be taken into consideration when recommending daily vitamin D intake given the potential for decreased vitamin D bioavailability in obese persons. In somewhat of a paradigm shift, they suggest that lower vitamin D levels may actually increase adiposity through secondary hyperparathyroidism. Furthermore, they hypothesize that low vitamin D may affect muscle mass directly or indirectly (via secondary hyperparathyroidism). With respect to the effect of vitamin D on muscle, the findings of Endo et al[11] are key. They found that vitamin D receptor–deficient mice, which are essentially vitamin D deficient, have smaller, more developmentally immature muscle fibers than those of wild-type mice. The finding of increased fat-free mass with higher 25OHD levels by Moschonis et al[8] is further supported by the clinical data of increased muscle weakness with lower 25OHD levels.[7] Finally, the relationship between vitamin D and IGF-1 is complex. Although there is in vitro evidence that IGF-1 and 1,25$(OH)_2$D upregulate each other, in vivo administration of growth hormone increases 1,25$(OH)_2$D but not 25OHD.[12,13] Therefore, it is unclear if the higher IGF-1 levels in the women with the highest 25OHD levels are due to an underlying physiologic relationship.

With respect to the authors' theory that low vitamin D may cause obesity, the cross-sectional nature of this analysis

represents the most critical limitation. As the authors discussed, obesity may lead to lower vitamin D levels through decreased vitamin D bioavailability. Alternatively, there may be no causal relationship between vitamin D and obesity, in either direction. As acknowledged by the authors, to answer the age old question of which came first, the chicken or the egg, or in this case the low vitamin D levels or the obesity, an interventional trial is needed to show that increasing vitamin D levels decreases fat mass and increases fat-free mass. In the absence of interventional trials, it will be challenging to advocate for increased vitamin D intake for the purpose of improving body composition or any of the other endpoints that epidemiologic data suggest are affected by vitamin D.

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Sherri-Ann M. Burnett-Bowie, MD, MPH
Endocrine Unit
Massachusetts General Hospital
Boston, MA

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