Expanding Roles of Vitamin D

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The traditional role of vitamin D involves calcium absorption and skeletal health. Two articles published recently in the Journal address two nontraditional roles of vitamin D. Pilz et al. (1) showed that vitamin D deficiency is associated with death from heart failure and sudden cardiac death in 3299 patients referred to coronary angiography in Germany. Circulating levels of 25-hydroxyvitamin D [25(OH)D] were measured at baseline, and the individuals were followed for up to 7.7 yr. At baseline, lower 25(OH)D level was associated with higher N-terminal pro-B-type natriuretic peptide levels and impaired left ventricular function, but not with angiographic coronary artery disease (CAD). After adjustment for cardiac risk factors, the individuals with low vitamin D levels [<25 nmol/liter (10 ng/ml)] were about three times more likely to die of heart failure and five times more likely to die of sudden cardiac death, compared with individuals with 25(OH)D levels of at least 75 nmol/liter (30 ng/ml). The risk for the combined endpoint of death due to heart failure and sudden cardiac death was higher in patients without CAD than those with CAD, suggesting a closer relationship between vitamin D deficiency and nonischemic diseases than with ischemic heart disease. Nonetheless, other studies suggest that vitamin D deficiency may increase risk of CAD, possibly by increasing calcification of coronary arteries (2).

The other study published in the Journal focused on vitamin D and skeletal muscle in 99 postmenarchal 12- to 14-yr-old girls in the United Kingdom (3). This study was cross-sectional and examined 25(OH)D concentrations in relation to results from jumping mechanography, a method that measures muscle force and power based on measurements from an individual’s ground reaction forces. The proximal muscles required for jumping (quadriiceps, gastrocnemius, soleus) appear to be the ones most affected by vitamin D deficiency, at least in older adults (4). This study found that 25(OH)D level was positively related to muscle power, force, velocity, and jump height, suggesting that muscle contractility may be affected by a girl’s vitamin D status.

The findings of both studies, relating vitamin D status to cardiac and skeletal muscle, are provocative and potentially clinically important if confirmed as causal associations in intervention studies. The designs of both studies require us to consider the possibility of reverse causation; that is, the outcomes of the study may have influenced vitamin D status, rather than vice versa. In the study by Pilz et al. (1), whereas the assessment of vitamin D was prospective in relation to the main endpoints of death from cardiac failure or sudden cardiac death, an inverse correlation existed at baseline between 25(OH)D level and measures of heart failure. Thus, it is possible that individuals with some degree of heart failure avoided outdoor activities, which could have limited their sun exposure and hence reduced their vitamin D status. The authors collected data on physical activity, and the reported associations remained after adjustment for physical activity. Although residual confounding from imperfectly measured physical activity might still have occurred, the fact that the associations for death due to heart failure or sudden cardiac death with low 25(OH)D were essentially unchanged after adjustment for physical activity, and remained strong, indicated that limited mobility leading to low 25(OH)D was unlikely to account entirely for the association. In the study of 25(OH)D and skeletal muscle contractility in girls, the potential influence of physical activity was not assessed.

Both findings can be placed in the context of a rapidly expanding literature that vitamin D level influences both cardiac and skeletal muscle function. Cardiac myocytes express the vitamin D receptor (VDR) and 1-α-hydroxylase and 24-hydroxylase, the enzymes required for the conversion of 1,25-dihydroxyvitamin D [1,25(OH)2D] from 25(OH)D and its subsequent breakdown. Treatment with 1,25(OH)2D leads to increased expression and nuclear localization of the VDR, increased expression of myotrophin, and decreased expression of atrial natriuretic peptide, c-myc (5) and human B-type natriuretic peptide (6). The induction of myocyte hypertrophy either in vitro or in vivo leads to an increase in VDR mRNA and protein levels, suggesting that the vitamin D system may act as an anti hypertrophic system in cardiac muscle. In addition, animal studies

Abbreviations: CAD, coronary artery disease; 25(OH)D, 25-hydroxyvitamin D; 1,25(OH)2D, 1,25-dihydroxyvitamin D; VDR, vitamin D receptor.
show that vitamin D is an important regulator of the renin-angiotensin axis, a system that helps regulate blood pressure, electrolyte and volume homeostasis. 1,25(OH)2D suppresses renin gene expression (7), and disruption of the VDR gene leads to elevated renin production, cardiac hypertrophy, and elevated blood pressure in mice (8). A strong inverse correlation has been observed between circulating 1,25(OH)2D levels and plasma renin activity in patients with essential hypertension (9).

In the study by Pilz et al. (1), an especially strong association (5-fold increase in risk) was observed between low 25(OH)D and the risk of sudden cardiac death. Insight to this finding may be provided by a recent finding of treatment of hemodialysis patients with activated vitamin D (calcitriol), which was associated with regression of cardiac hypertrophy and a reduction of QTc dispersion, a risk factor for sudden cardiac death; these changes were not seen in a similar group of untreated patients (10). Cardiac death rate is especially high in chronic renal failure patients, perhaps in part because the profound functional vitamin D deficiency that these patients suffer is due primarily to loss of renal conversion of 25(OH)D to 1,25(OH)2D. In nonrenal patients with severe vitamin D deficiency, similar but less extreme processes involving the cardiovascular system could be occurring.

The study of vitamin D status and muscle function by Ward et al. (3) extends previous findings of 25(OH)D status and skeletal muscle function in elderly adults. As for cardiac muscle, skeletal muscle expresses VDR (11), and deletion of the VDR gene in mice disrupts expression of myoregulatory transcription factors and impairs skeletal muscle development (12). Activation of the VDR in myocytes leads to protein synthesis and muscle cell growth (13) and to improved muscular function based on intervention studies in humans (14). In adults aged 60 or older, an association exists between 25(OH)D concentrations and lower extremity function, based on the 8-foot walk and the sit-to-stand tests, particularly at levels below 40 nmol/liter (16 ng/ml) (15). The improvement of muscular function is likely to explain why supplementation with vitamin D may reduce the risk of falling in older adults and may contribute to the role of vitamin D in the reduction of bone fractures (16). Although children and adolescents are not normally at risk for osteoporotic fractures, Ward et al. (3) point out that muscle-generated forces are required to optimally affect the development of peak bone strength.

A notable feature of the two studies on vitamin D and cardiac and skeletal muscle is that they were conducted in populations living at relatively high latitudes (Manchester, UK, 53° 30’N; Ludwigshafen, Germany, 49° 28’N) which likely contributed to poor vitamin D status. In the study by Pilz et al. (1) conducted in Germany, only 10% of the population had 25(OH)D levels of at least 75 nmol/liter, and 24% had levels below 25 nmol/liter, which can be considered the severely deficient range. In this population, PTH levels decreased and 1,25(OH)2D levels increased across the entire range of 25(OH)D. Inadequate substrate leading to low 1,25(OH)2D levels despite a compensatory rise in PTH signals a severe vitamin D deficiency. In the United Kingdom study of adolescent girls, the median 25(OH)D level was 21.3 nmol/liter (8.5 ng/ml), indicating that the majority of girls were in the severely deficient range. Very few of the girls had levels of 75 nmol/liter or greater.

An increasing number of studies are documenting that in most populations, severe vitamin D deficiency (<25 nmol/liter) is not uncommon (17–19), and suboptimal vitamin D (<75 nmol/liter) may be the norm rather than the exception at high latitudes. Meanwhile, the list of nontraditional vitamin D deficiency-associated diseases and conditions continues to grow; these may include impaired bone and musculoskeletal health, various cancers, CAD, high blood pressure, sudden cardiac death, heart failure, autoimmune diseases (including multiple sclerosis and type 1 diabetes), and infectious diseases (17). Although questions remain regarding the causal nature of these associations, at least some meta-analyses of randomized trials of vitamin D supplementation have shown statistically significant reductions in total mortality (20), falls and nonvertebral fractures (16), and a small randomized trial suggested a benefit on cancer risk (21). Vitamin D deficiency also increases PTH levels (16), which likely has adverse bone effects and possibly other negative consequences (22, 23).

We do not know all of the roles of vitamin D. But we do know that many types of tissues in humans express the VDR and the main enzymes that metabolize vitamin D, and in vitro and in vivo models suggest that these have functional roles. We also know that it is likely throughout most of human evolution when the vitamin D system was developing that the level of 25(OH)D can be inferred to be around 150 nmol/liter (60 ng/ml) or higher (24). In the studies reviewed here and in numerous other populations, many individual have levels of 25(OH)D that are 5- to 10-fold lower than this. We also know that a large body of observational data and a few intervention studies suggest multiple potential benefits, with risk of adverse consequences minimized at least to levels around 75 nmol/liter; whether risks would be minimized at higher levels of 25(OH)D than 75 nmol/liter is unknown largely because relatively few individuals in modern societies attain such levels.

Four misconceptions have hampered attempts to improve vitamin D status. These are that the only function of vitamin D is on mineral homeostasis, that intakes as low as 400 IU/d are adequate, that intakes higher than 2000 IU/d are toxic, and that sun exposure is uniformly deleterious. Yet, we now know that many diverse cell types have the vitamin D metabolic machinery intact, and vitamin D has multiple functions. Also, we know that 400 IU/d, the level that prevents rickets in infants is not adequate for adults with body masses 20 to 30 times larger, particularly when sun-induced vitamin D production is low. We also know that 2000 IU/d as the upper tolerated dose for adults has little basis, and that the upper limit for vitamin D consumption for adults should be probably be at least 10,000 IU/d (25). Rather than the upper tolerated limit, 2000 IU/d may turn out to be the recommended intake for adults. Finally, whereas excess sun exposure certainly has negative consequences especially for light-skinned individuals, essentially all of the vitamin D-associated conditions summarized above have lower rates in sunnier climates, and within populations, lower rates of these conditions are seen among those with 25(OH)D levels of at least 75 nmol/liter—levels that are currently achievable mainly through sunlight exposure due to limited intake.

The vitamin D system is complex, influencing expression of more than 200 genes, and is involved in many tissues—anything
approaching even a semicomplete understanding is many decades away. Given our current understanding, the relevant question from a medical and public health perspective is: should we be concerned enough about the high prevalence of vitamin D deficiency to warrant recommending intakes of 1000 to 2000 IU/d of vitamin D?

Acknowledgments

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References