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Vitamin D
Its role in disease prevention

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Evidence that vitamin D reduces the risk of many types of disease is increasing exponentially. In 2011, 3,100 publications with "vitamin D" in the title or abstract were published, up from 2,606 in 2010, 1,303 in 2005, and 796 in 2000. A committee operating under the auspices of the Institute of Medicine (IOM) of the US National Academies reviewed the evidence for beneficial effects of vitamin D. Their report, issued at the end of 2010,[1] found what they considered to be strong evidence for only one health outcome: skeletal health. They considered beneficial evidence only from published randomized controlled trials (RCTs) focused mainly on skeletal health. In contrast, to justify concern about higher vitamin D intake and serum 25(OH)D concentrations, they used data from nested case-control studies reporting U-shaped outcomes of prediagnostic serum 25-hydroxyvitamin D [25(OH)D] for cancer and all-cause mortality rates. They set the daily recommended intake of vitamin D at 600–800 IU for most children and adults and defined vitamin D sufficiency as a serum 25(OH)D level above 20 ng/ml (50 nmol/l). They also set a daily upper intake of 4,000 IU of vitamin D_3 and called for more RCTs to determine nonskeletal health effects. As of this writing, more than 130 journal publications have criticized the IOM report as being too conservative. One summarized the problems succinctly: "The IOM recommendations for vitamin D fail in a major way on logic, on science, and on effective public health guidance. Moreover, by failing to use a physiological referent, the IOM approach constitutes precisely the wrong model for development of nutritional policy."[2]

This special issue of *Dermato-Endocrinology* includes a collection of papers addressing the role of vitamin D in reducing risk of nonskeletal diseases. One paper[3] addresses the IOM findings directly, pointing out the report's many analysis problems and referring to a later vitamin D guideline statement from the Endocrine Society.[4] To maintain serum 25(OH)D levels above 30 ng/ml for preventing and treating vitamin D deficiency, this society's guidelines recommend 400–1,000 IU for children and 1,500–2,000 IU for adults.

Much of the evidence for beneficial effects of vitamin D comes from ecological and observational studies. Such studies are highly appropriate because vitamin D is a natural substance that humanity has lived with throughout history. The importance of vitamin D is underscored by the fact that skin pigmentation varied as humans moved out of Africa, becoming very pale in northern Europe. Skin pigmentation varies with solar ultravoilet (UV) doses, dark enough to reduce the risks from free radical production and folate destruction, light enough to permit adequate vitamin D production.[5]

This issue includes one ecological study, of cancer mortality rates in California for 1950–1964.[6] Using multiple linear regression analyses, this study found significant inverse correlations with nonmelanoma skin cancer mortality rate during 1950–1964 for eight types of cancer for males: bladder, brain, colon, gastric, prostate, and rectal cancer; multiple myeloma; and non-Hodgkin lymphoma. The study found no such correlations for females. After that period, no inverse correlation existed between skin cancer and other types. Until the 1960s, people considered the sun something to enjoy, not to fear, and sunscreen and sun avoidance had not yet been widely recommended.

Another paper on cancer in this issue reviews the evidence of disparities in cancer survival rates for American blacks and whites. This report finds that disparities emerging after consideration of socioeconomic status, stage at time of diagnosis, and treatment for about a dozen types of cancer are likely due to differences in serum 25(OH)D concentrations.[7] Survival disparities ranged from about 10–50%.

A powerful but little-used method to assess the causality of a proposed risk-modifying factor is to see whether it satisfies Hill's criteria for causality in a biological system.[8] These criteria are useful in reviewing the totality of evidence regarding a suspected agent and disease outcome. The more important criteria include strength of association,

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consistency, identifying mechanisms, and experimental verification. Not all criteria need be satisfied, but the more that are, the stronger the case. For vitamin D and cancer, RCTs are generally considered the best choice for experimental confirmation. Mohr and colleagues[9] reviewed the evidence regarding vitamin D in reducing risk of breast cancer, concluding that the evidence largely satisfied the criteria for a causal role.

The IOM committee called for RCTs to firmly establish the benefits of vitamin D for nonskeletal effects.[1] As this issue discusses, conducting RCTs with vitamin D can have many pitfalls.[10] An important problem that Lappe and Heaney's paper discusses is that serum 25(OH)D concentrations have a sigmoid relationship with respect to oral vitamin D intake: for a given dose, increases are much larger for people with low initial concentrations than for people with higher concentrations. In addition, it is serum 25(OH)D concentration, not vitamin D intake, that affects risk of disease. Thus, unless serum 25(OH)D concentrations are measured at least two or three times during the study, interpreting the results of such RCTs is difficult.

One problem with prospective observational studies is that most use a single serum 25(OH)D concentration taken at time of enrollment to measure vitamin D status. This approach underestimates the benefit of vitamin D due to changes over time of both absolute and relative serum 25(OH)D concentrations, as shown previously for breast and colorectal cancer.[11] In the paper by Grant,[12] when the hazard ratio for mortality rate for a 20-nmol/l increase in 25(OH)D concentration for 12 studies is plotted vs. follow-up time, the linear extrapolation to zero follow-up time indicates a 28% reduction in all-cause mortality rate, compared with 8% for the average of all 12 studies without considering follow-up time. Thus, the beneficial effects of vitamin D may be much higher than is apparent according to prospective studies.

A review of the evidence of vitamin D's role in reducing risk of the metabolic syndrome and its sequelae, type 2 diabetes mellitus and cardiovascular disease (CVD)—by the researcher who first proposed the link[13]—found that more than 40 cross-sectional and prospective studies largely support a beneficial role but that RCTs have not yet supported this role.[14] However, vitamin D supplementation can increase survival of those with cardiac disorders.[15]

Juzeniene and Moan[16] discussed beneficial effects of UV radiation other than vitamin D production. Several human skin diseases, including psoriasis, vitiligo, atopic dermatitis and localized scleroderma, can be treated with solar radiation (heliotherapy) or artificial UV radiation (phototherapy). One non-vitamin D effect of UVA is liberation of nitric oxide (NO) from NO derivatives such as nitrite and nitrosothiols in the skin. NO can lower blood pressure. NO may also have antimicrobial effects and act as a neurotransmitter. UV also releases endorphins, which may be one reason that being in the sun is pleasurable. However, although the paper notes that UV may reduce the risk of multiple sclerosis through non-vitamin D mechanisms, it reports no evidence that non-vitamin D effects of UV reduce risk of internal cancers.

Sorenson and Grant[17] proposed the hypothesis that vitamin D deficiency may be a risk factor for erectile dysfunction (ED), as well as a risk for CVD for those who develop ED. About half the cases of ED are linked to vascular disease. Aspects of vascular disease such as vascular endothelial damage, vascular calcification, and hypertension play a role in ED. Whether increasing serum 25(OH)D concentrations could reduce the severity of ED is not clear. However, because many men diagnosed with ED are diagnosed with CVD within a few years, and because vitamin D deficiency is linked to risk of CVD and taking vitamin D supplements can reduce risk of CVD, men with ED would probably benefit from increasing serum 25(OH)D concentrations.

Researchers have shown renewed interest in the role of optimal vitamin D status in the prevention and treatment of infections. The study by Grossmann and colleagues[18] examined the effects of a large dose of cholecalciferol given to subjects with cystic fibrosis at the time of a hospitalization for an acute respiratory infection. They found that 250,000 IU of cholecalciferol rapidly restored vitamin D status into the optimal range and was associated with improved survival, improved recovery of lung function, and improved hospitalization rates. Kempker and colleagues[19] reviewed the relationship between vitamin D status and sepsis. They highlight several studies in vitro and in vivo that support early epidemiologic and intervention studies pointing to an important role for vitamin D in the critically ill patient with infection.

Vitamin D deficiency is a common feature of chronic kidney disease (CKD). Current guidelines for vitamin D therapy from the National Kidney Foundation have not proven universally successful and have not addressed earlier stages of CKD.[20] Alvarez and colleagues[21] systematically reviewed vitamin D repletion in subjects with early CKD, finding differences in vitamin D repletion regimens and in measured outcomes. In general, ergocalciferol was less effective than cholecalciferol, and most studies found that correcting vitamin D status required a daily dose of greater than 2,000 IU.

The paper by Gröber and Kisters[22] reviews the interaction between pharmaceutical drugs and vitamin D. Vitamin D can improve the efficacy and reduce some of the adverse side effects of several types of drugs. The categories of drugs discusses are antiepileptic drugs glucocorticoids, bisphosphonates, antiretroviral drugs, anti-estrogens, cytostatic agents, antihypertensive drugs, and antituberculotic drugs. Some of the action occurs through the Pregnane X receptor (PXR), which plays an important role in detoxifying xenobiotics and drugs. A number of drugs activate the PXR. The PXR can control the expression of genes normally controlled by vitamin D receptors.

The paper by Youssef and colleagues[23] discusses the potential role of vitamin D in reducing risk of hospital-acquired infections, such as pneumonia, bacteremias, urinary tract infections, and surgical site infections. An accompanying editorial by McCarthy[24] endorses the suggestion that vitamin D status be assessed and corrected in hospital patients.

Finally, given the epidemiologic and preclinical studies linking vitamin D status and two immune-mediated diseases, asthma

and lupus, Brown and colleagues[22] and Singh and colleagues[23] have reviewed the evidence between vitamin D status and these diseases, respectively. Brown's group[25] notes that several studies of pregnant women and their offspring suggest that vitamin D deficiency may predispose an infant to future risk of wheezing disorders. Further, the authors report studies demonstrating an association between vitamin D status and asthmatic control. Singh and colleagues[26] note several cross-sectional clinical studies demonstrating an association between vitamin D status and control of lupus. Given that studies have associated vitamin D deficiency with CVD and osteoporosis, they make recommendations for vitamin D intake in patients with lupus.

This special issue of *Dermato-Endocrinology* contains several papers that review the evidence for the beneficial effects of solar ultravoilet-B (UVB) irradiance and vitamin D, as well as some that break new ground. We hope that publication of this issue will both encourage additional research and help move health policy makers toward greater acceptance of both UVB irradiance and higher serum 25(OH)D concentrations.

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