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Biol Res Nurs published online 17 January 2011
DOI: 10.1177/1099800410391243

Biological Research for Nursing
000(00) 1-14

DOI: 10.1177/1099800410391243
http://brn.sagepub.com
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Requirements for Vitamin D Across the Life Span

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Adequate provision of vitamin D has been found, in ecological, cross-sectional, and observational studies, to be associated with reduction in the risk of many types of cancer, cardiovascular diseases (CVDs), autoimmune diseases, diabetes mellitus types 1 and 2, neurological disorders, several bacterial and viral infections, and adverse pregnancy outcomes in addition to the classical bone disorders of rickets and osteomalacia. Furthermore, investigators have found adequate repletion and increased intakes of vitamin D to be associated with reduced all-cause mortality rates. These findings have been supported by the limited number of properly conducted randomized controlled trials (RCTs) that used more than 400 IU/day of vitamin D. This review presents an overview of the role of vitamin D for the promotion of health for the more important vitamin D-related diseases and conditions. Serum 25-hydroxyvitamin D concentrations of 30–60 ng/ml, corresponding to oral intake or skin production of 1,000–4,000 IU/day of vitamin D, appear necessary in adults for avoidance of hypovitaminosis D-related ill health. People of all ages are encouraged to obtain more vitamin D from judicious exposure to sunshine (for ultraviolet B [UVB] irradiation) or from regular vitamin D supplements because dietary sources do not provide sufficient vitamin D to prevent any health risks other than those of rickets and osteomalacia.

Keywords
bones, cancer, cardiovascular disease, diabetes, infections, pregnancy outcomes, ultraviolet B, vitamin D

Almost 300 years after the recognition of its importance for prevention of rickets (Gibbs, 1994; Rajakumar, Greenspan, Thomas, & Holick, 2007), vitamin D is finally gaining recognition as being essential for optimal health (Holick, 2007). Emerging science has linked higher solar ultraviolet B (UVB) irradiance, increased oral intakes of vitamin D, and higher circulating concentrations of serum 25-hydroxyvitamin D (25[OH]D) to reduced risk of many chronic and infectious diseases including at least 20 types of cancer (Boscoe & Schymura, 2006; Grant, 2007; Grant & Garland, 2006), both bacterial (Bikle, 2008) and viral infections (Cannell et al., 2006; Cannell, Hollis, Zasloff, & Heaney, 2008), autoimmune diseases (Fernandes de Abreu, Eyles, & Feron, 2009), both types 1 and 2 diabetes mellitus (Mohr, Garland, Gorham, & Garland, 2008; Pittas et al., 2006), cardiovascular diseases (CVDs; Dobnig et al., 2008; Giovannucci, Liu, Hollis, & Rimm, 2008), dementia (Grant, 2009b), and osteoporotic fractures (Bischoff-Ferrari et al., 2005). Those with higher serum 25(OH)D levels have significantly reduced mortality rates (Ginde, Scragg, Schwartz, & Camargo, 2009). In addition, better vitamin D status is associated with increased fertility (Stumpf & Denny, 1989) and better pregnancy outcomes (Bodnar, Simhan, et al., 2007; Merewood, Mehta, Chen, Bauchner, & Holick, 2009). In polycystic ovary syndrome, dominant follicle formation and ovulation can be restored by supplementation with vitamin D in deficiency (Rashidi, Haghollahi, Shariat, & Zayerii, 2009; Thys-Jacobs, Donovan, Papdopoulos, Sarrel, & Bilezikian, 1999).

Unfortunately, public health recommendations on vitamin D requirements and solar UVB irradiance have not kept pace with the emerging scientific findings (IOM, 2010; Ross et al., 2010). There appears to be some inertia in the reaction to the evidence, which has resulted in a delay in the paradigm change required for cancer in particular (Grant & Boucher, 2009). This report is an effort to reach nurses, who can then pass the information on to other health care professionals and to their patients. In it, we examine the roles of vitamin D, the evidence for various benefits from epidemiological studies and some of the mechanisms for vitamin D's effects. We conclude with recommendations on the vitamin D intake and serum 25(OH)D concentration required for optimal health.

Physiology of Vitamin D

Vitamin D is produced in the skin by the action of UVB irradiance (wavelength 290–315 nm) on 7-dehydroxycholesterol in

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the deeper epidermis, converting it to pre-vitamin D3. This compound then undergoes a thermal transformation to vitamin D3 (cholecalciferol) and is transported on specific serum D-binding proteins to the liver, where it is hydroxylated to become 25(OH)D, the most common circulating metabolite of vitamin D. The kidney and many other organs can then further hydroxylate 25(OH)D to produce 1,25-dihydroxyvitmin D [$1,25(OH)_2D$ or calcitriol], the hormonal version of vitamin D. $1,25(OH)_2D$ can activate vitamin D receptors (VDRs). The actions of VDRs include modulation of genes affecting the regulation of the immune system's B and T lymphocytes and of cells in hair follicles, muscle, adipose tissue, bone marrow, and certain cancer cells (Norman, 2006). Nongenomic rapid response effects also occur through binding to non-nuclear VDRs; such effects include induction of the rapid intestinal absorption of calcium (transcaltachia), secretion of insulin by pancreatic beta-cells, opening of voltage-gated Ca^2 and Cl^- channels in osteoblasts and the rapid migration of endothelial cells (Norman, 2006). The complexities of the actions of vitamin D in the body are still being worked out, for example, the vitamin D sterol–vitamin D receptor ensemble model (Mizwicki & Norman, 2009).

Because $1,25(OH)_2D$ is the active metabolite of vitamin D and serum concentrations of $1,25(OH)_2D$ are quite tightly regulated by feedback mechanisms involving both parathyroid hormone and serum calcium levels (Need, Horowitz, Morris, & Nordin, 2000), it was initially puzzling that different concentrations of serum 25(OH)D should result in different health and disease outcomes. However, when it was found that many organs have the ability to convert 25(OH)D to $1,25(OH)_2D$ locally by producing their own vitamin D-activating 1-α-hydroxylase (Zehnder et al., 2001), it resolved the mystery (Holick, 2008). We will delve further into the mechanisms by which vitamin D induces its effects with each health or disease outcome discussed below.

Oral vitamin D3 is bioidentical to vitamin D3 produced in the skin and generally comes from UVB-irradiated sheep's wool lanolin or fish oil. Yeast and mushrooms produce ergocalciferol (vitamin D2). Vitamin D2 is generally considered to be less effective and thought to stay in the blood stream for a shorter time (Houghton & Vieth, 2006). In this article, we use *vitamin D* as a general term and *vitamin D3* and *vitamin D2* when referring to these specific compounds.

Since the understanding of the health benefits of vitamin D is expanding rapidly, the categorization of serum 25(OH)D level into optimal, sufficient, and deficient is somewhat in flux. In this article, we consider levels above 40 ng/ml (100 nmol/l) but below 80 ng/ml to be optimal, between 30 ng/ml and 40 ng/ml to be sufficient, <30 ng/ml but >12 ng/ml to be insufficient, and <12 ng/ml to be deficient.

Musculoskeletal Systems

The adolescent years are a period of rapid growth. In a study in Ohio, researchers found that serum 1,25(OH)2D concentrations were at their highest during the pubertal growth spurt (sexual maturity index 3–4, age 11–13 years) and correlated with both peak skeletal calcium accretion (g/year) and total body and forearm bone mass accumulation rates (Ilich et al., 1997). Evidence is currently emerging that better maternal vitamin D repletion in pregnancy predicts increases in bone strength in children at the age of 9 (Javaid et al., 2006; Sayers & Tobias, 2009).

Bone Development, Muscles, and Neuromuscular Control

In addition to vitamin D's role in promoting healthy bones and bone growth, it has proved to reduce the risk of stress fractures in healthy young female military recruits (Bouillon, 2008). The fact that vitamin D supplementation in hypovitaminosis D increases muscle strength in both younger and older people may explain why supplementation reduces the rates of falls in the elderly (Ceglia, 2008; Moreira-Pfrimer, Pedrosa, Teixeira, & Lazaretti-Castro, 2009).

Primary osteomalacia, a classic bone disorder of vitamin D deficiency, is seen rather than rickets once growth is complete and can occur from the teens to old age. Presentation is usually with nonspecific "aches and pains" and proximal muscle weakness. Sometimes it is detected on isotope bone imaging by the finding of local hot spots (pseudofractures) or when avidity of bone uptake precludes kidney uptake of tracer despite normal renal function. This condition, therefore, is often missed until the typical pseudofractures become painful. It is rapidly cured by vitamin D treatment (Mawer & Davies, 2001). Untreated, the already poorly calcified bone softens and the pelvis may flatten, leading to pelvic outlet narrowing. The resultant obstruction of labor can prove fatal to both mother and infant (Pillai, 1993).

Falls and Hip Fractures

Risk of falls and "fragility" fractures are a major concern for elderly women. There are many risk factors for these problems including weak bones, poor muscle strength, poor neuromuscular control, and impaired cognitive function. Vitamin D appears to be protective against all these factors (Annweller et al., 2009; Ceglia, 2008; Moreira-Pfrimer et al., 2009; Staud, 2005). Vitamin D supplementation at 700–800 IU/day can reduce hip fracture rates by about 25% (Bischoff-Ferrari et al., 2005; Trivedi, Doll, & Khaw, 2003).

Cancer

Cancer is one of the most common diseases in the United States. It was estimated that there would be 1,480,000 new cases and 560,000 deaths in 2009 (Jemal et al., 2009). Vitamin D-sensitive cancers comprise about 80% of estimated new cases and deaths from cancer in the United States for 2009.

There is strong evidence from ecological, cross-sectional, and observational studies that levels of solar UVB irradiation and vitamin D are inversely correlated with incidence and

mortality rates for a number of cancers. The UVB–vitamin D–cancer hypothesis was originally proposed by Garland and Garland (1980) based on the connection they observed between hours of annual sunlight and colon cancer mortality rates in the United States. Since then ecological and observational studies have identified about 20 types of cancer for which there is reasonable evidence that solar UVB and vitamin D reduce the risk of incidence and/or death: bladder, breast, colon, endometrial, esophageal, gallbladder, gastric, lung, ovarian, pancreatic, prostate, rectal, renal, and vulvar cancer; melanoma; and both Hodgkin's and non-Hodgkin's lymphoma (Boscoe & Schymura, 2006; Chen, Hu, et al., 2010; Giovannucci, Liu, Rimm, et al., 2006; Gorham et al., 2007; Grant, 2002b; Grant, 2007; Grant & Garland, 2006).

Ecological studies are ideally suited to study risk-modifying factors for cancer, such as diet and UVB–vitamin D. Much of the risk for cancer occurs in the first 20 years of life, and ecological studies integrate the effects of risk-modifying factors over the entire lifetime starting at the time of conception. For example, in a multi-country study, investigators found that dietary intake of total fat and animal fat were highly correlated with mortality rates for breast, colon, ovarian, prostate, and other cancers (Armstrong & Doll, 1975). It took 30 years for cohort studies to confirm this finding, and they were able to do so only because they finally enrolled younger people in the studies (Linos, Willett, Cho, Colditz, & Frazier, 2008). In addition, there is a long lag time between cancer initiation and detection. A recent study reported a 20-year lag between initiation and detection for pancreatic cancer (Campbell et al., 2010). The importance of vitamin D is that it could reduce the risk of cancer initiation rather than simply slowing or halting progression. Solar UVB is the primary source of vitamin D for most people. In summer, casual UVB irradiance is sufficient to produce 1,500 IU/day in England for those aged 45 years (Hypponen & Power, 2007). Those of similar age living in the south, such as in most of the United States, should be able to make more vitamin D. As another example of the usefulness of ecological studies in examining risk-modifying factors for cancer, researchers found higher solar UVB irradiance early in life to be correlated with reduced risk of prostate cancer (John, Schwartz, Koo, Wang, & Ingles, 2007) but have not found a similar correlation with prediagnostic serum 25(OH)D levels measured 5–10 years prior to prostate cancer (Gupta et al., 2009). In fact, while prediagnostic serum 25(OH)D level has been found to be inversely correlated with incidence of breast and colorectal cancer (Grant, 2010c) and ovarian cancer (Toriola et al., 2010), such a correlation has not been found for many other cancers (Helzlsouer, 2010). Finally, the availability of data on major cancer risk-modifying factors at the state or country level allows researchers conducting ecological studies to reduce the risk of confounding by other unidentified causal factors (Grant & Garland, 2006).

Support for a role of vitamin D in reducing the risk of cancer is found in the only RCT of vitamin D to have a significant impact on cancer risk. Among postmenopausal women living in Nebraska, those taking 1,100 IU/day of vitamin D and 1,500 mg/day of calcium had a 77% reduction in all-cancer incidence between the ends of the first and fourth years of the trial (Lappe, Travers-Gustafson, Davies, Recker, & Heaney, 2007). Those taking calcium without vitamin D had a 40% reduction. This trial is the only one to date examining such high doses of vitamin D. As it showed, calcium also reduces the risk of cancer, and a review of the benefits of calcium in reducing the risk of cancer was published recently (Peterlik, Grant, & Cross, 2009).

The mechanisms whereby vitamin D can reduce the risk of cancer are well known and include effects on cellular differentiation and proliferation, angiogenesis, and metastasis (Ingraham, Bragdon, & Nohe, 2008). Other researchers have reported a new mechanism for the role of vitamin D in cancer risk reduction in which vitamin D metabolites prevent disjunction of cells and are beneficial in other phases (C. F. Garland, Gorham, Mohr, & Garland, 2009).

Breast cancer risk is a concern for women from the age of 40 years onward. Although diet early in life with a high fraction of energy derived from animal products is an independent risk factor, along with alcohol later in life (Grant, 2002a), a growing body of research reports that vitamin D reduces the risk of breast cancer. The original epidemiological finding was from an ecological study (F. C. Garland, Garland, Gorham, & Young, 1990), but now there are also supporting cross-sectional studies (John, Schwartz, Koo, Wang, & Ingles, 2007) as well as many observational studies that include premenopausal women (Abbas, Chang-Claude, & Linseisen, 2009). Meta-analysis of observational studies indicates that serum 25(OH)D levels of about 40 ng/ml reduce the risk of breast cancer incidence by 50% compared to serum levels of 12 ng/ml and that the relationship is nonlinear, that is, additional reductions occur at a slower rate for higher serum 25(OH)D levels (C. F. Garland, Gorham, et al., 2007; Grant, 2010c). See, also, the recent meta-analysis by Chen, Clements et al. (2010). There are also a number of recent reviews on the UVB–vitamin D–cancer hypothesis (C. F. Garland et al., 2006; Grant & Mohr, 2009; Mohr, 2009).

Based on the studies just discussed, as well as four recent reports of greater cancer survival rates for those with higher serum 25(OH)D levels—all cancers (Pilz, Dobnig, Nijpels et al., 2008), colorectal cancer (Ng et al., 2008), breast cancer (Goodwin, Ennis, Pritchard, Koo, & Hood, 2008), and non-Hodgkin's lymphoma (Drake et al., 2010)—I (WBG) have proposed that those diagnosed with cancer should have their serum 25(OH)D levels raised as part of their treatment (Grant, 2010a). Optimal levels for cancer prevention seem to be above 40 ng/ml (Grant, 2010c).

The question arises as to how strong the evidence is that solar UVB and vitamin D reduce the risk of cancer, especially since there has only been one RCT involving sufficient vitamin D intake to have a significant effect (Lappe et al., 2007). In fact, the International Agency for Research on Cancer (IARC) issued a report very critical of the UVB–vitamin D–cancer hypothesis (International Agency for Research on Cancer [IARC] Working Group, 2008). As I (WBG) discussed at

length in a critique of this report (Grant, 2009a), the IARC Working Group, comprised primarily of skin cancer experts, committed many errors and omissions in reaching their conclusion that there was good evidence for vitamin D reducing the risk of only one type of cancer, colorectal cancer. In another paper, I (WBG) argued that the evidence for the UVB–vitamin D–cancer hypothesis largely satisfies Hill's criteria for causality in a biological system for breast and colorectal cancer and reasonably well for several other types of cancer (Grant, 2009c).

CVDs

CVDs affect more Americans than any other diseases. The American Heart Association estimated that 81 million Americans had CVD in 2006 and 831,000 died (American Heart Association, 2010). Among the CVDs, coronary heart disease affected 17.6 million, stroke 6.4 million, high blood pressure 74.5 million, and heart failure 5.8 million. Among the deaths, 425,000 were from coronary heart disease, 137,000 from stroke, 57,000 from high blood pressure, and 283,000 from heart failure.

Several observational studies have been published since 2008 showing that those with higher serum 25(OH)D concentrations have lower risk of CVD incidence or lower mortality rates. In the Framingham Heart Study, individuals with serum 25(OH)D levels less than 15 ng/ml had a multivariable-adjusted hazard ratio (HR) of 1.62 (95% confidence interval [CI] [1.11, 2.36], $p = .01$) for incident cardiovascular events compared with those with 25(OH)D levels of at least 15 ng/ml (Wang et al., 2008). A study in Germany found a significant reduction in risk of stroke with higher serum 25(OH)D levels (Pilz, Dobnig, Fisher et al., 2008). A review of data from the Health Professionals Follow-Up Study found a relative risk of acute myocardial infarction of 2.09 (95% CI, [1.24, 3.54], $p_{trend} = .02$) for 25(OH)D < 10 ng/ml versus >30 ng/ml (Giovannucci et al., 2008). Another cohort study found an adjusted HR for cardiovascular death of 2.36 (95% CI [1.17, 4.75]) for 25(OH)D < 10.0 ng/ml versus ≥ 40.0 ng/ml; Ginde, Scragg, et al., 2009). A preliminary meta-analysis using data from six recent articles (Dobnig et al., 2008; Ginde, Scragg, et al., 2009; Giovannucci et al., 2008; Kilkkinen et al., 2009; Melamed, Michos, Post, & Astor, 2008; Semba et al., 2010) found that the serum 25(OH)D level–CVD mortality relations are similar to those for breast cancer. A recent article reported a meta-analysis of CVD based on cohort, case–control, and cross-sectional studies and found an odds ratio (OR) of 0.67 (95% CI [0.55, 0.81]) with respect to high versus low serum 25(OH)D levels (Parker et al., 2010).

Hypertension affects people at all ages but becomes more common with advancing age. While many factors contribute to hypertension, vitamin D can reduce blood pressure, especially in younger people and before hypertension has become established, probably through suppression of renin formation, which reduces renin–angiotensin system (RAS) activity (Li et al., 2002; Pilz et al., 2009). Forman and colleagues (2007) examined data from two prospective cohort studies including 613 men from the Health Professionals' Follow-Up Study and 1,198 women from the Nurses' Health Study with measured 25(OH)D levels followed for 4–8 years as well as two additional prospective cohort studies involving 38,388 men and 77,531 women. Researchers followed predicted 25(OH)D levels based on relations between serum 25(OH)D and factors such as skin pigmentation, oral intake, geographical location, and leisure time spent out of doors for 16–18 years.

During 4 years of follow-up, the multivariable relative risk of incident hypertension among men whose measured plasma 25(OH)D levels were <15 ng/ml (i.e., vitamin D deficiency) compared with those whose levels were ≥30 ng/ml was 6.13 (95% CI [1.00, 37.8]). Among women, the same comparison yielded a relative risk of 2.67 (95% CI [1.05, 6.79]). The pooled relative risk combining men and women with measured 25(OH)D levels using the random-effects model was 3.18 (95% CI [1.39, 7.29]; Forman et al., 2007, p. 1063).

Note that the predicted serum 25(OH)D levels in the Forman study were based on an approach developed by Giovannucci, Liu, Rimm, and colleagues (2006).

Two recent reviews summarize possible mechanisms whereby vitamin D protects against CVD (Gouni-Berthold, Krone, & Berthold, 2009; Judd & Tangpricha, 2009), including reduced blood pressure, and reduced risk of calcification of the arteries. In addition, reduction in matrix metalloproteinases (MMPs) such as MMP9 may play a role (Timms et al., 2002). While these results are strongly suggestive of a beneficial role of vitamin D in reducing the risk of cardiovascular events, there have not yet been any RCTs conducted to confirm these cross-sectional and observational study findings.

Metabolic Diseases

The incidence and prevalence rates for type 2 diabetes mellitus (T2DM) are increasing rapidly in the United States (Sloan, Bethel, Ruiz, Shea, & Feinglos, 2008) in both children and adults. In 2006, an estimated 17 million had physician-diagnosed diabetes, 6 million had undiagnosed diabetes, and 57 million had prediabetes (American Heart Association, 2009). The primary risk factors for diabetes are poor diet (Brunner et al., 2008) and obesity (Deshpande, Harris-Hayes, & Schootman, 2008), but review of the earlier literature shows that vitamin D promotes both insulin sensitivity and insulin secretion in animals and in humans (Boucher, 1998). Furthermore, baseline vitamin D status was an independent predictor of T2DM risk 10 years later in the prospective Medical Research Council-Ely study (Forouhi, Luan, Cooper, Boucher, & Wareham, 2008). Several studies have addressed the role of vitamin D and calcium in reducing the risk of T2DM. A recent meta-analysis of nine studies found that risk of diabetes was 0.45 (95% CI [0.25, 0.82]) for high versus low serum levels of 25(OH)D (Parker et al., 2010).

Possible mechanisms for the beneficial roles of calcium and vitamin D in reducing the risk of T2DM include increased pancreatic β-cell function and suppression of the local pancreatic RAS, which has been shown to increase islet damage and also insulin resistance in hyperglycemia (see discussion on

hypertension in "CVDs," above; Boucher, Mannan, Noonan, Hales, & Evans, 1995; Leung & de Gasparo, 2006); reductions in insulin resistance (Nagpal, Pande, & Bhartia, 2009; von Hurst, Stonehouse, & Coad, 2010); and suppression of inflammation by modulation of the generation and effects of cytokines (Liu et al., 2009; Pittas, Harris, Stark, & Dawson-Hughes, 2007; Timms et al., 2002).

Infectious Diseases

One unexpected benefit of a sufficiency of vitamin D appears to be reduced risk of bacterial and viral infections. The hormonal version of vitamin D, $1,25(OH)_2D$, induces production by various white cells of antimicrobial polypeptides including human cathelicidin, or LL-37, which has both antimicrobial and anti-endotoxin effects (Mookherjee, Rehaume, & Hancock, 2007), and, subsequently, alpha-defensin (Zheng et al., 2007). LL-37 participates as part of the body's innate immune system, which can be important before the adaptive immune system has a chance to develop either through antibodies acquired through breast feeding or in response to contact with microbes and response by the T-cells (McDade, 2003). In addition, 1,25(OH)2D affects the production of cytokines, inducing a shift from the production of T-helper 1 (Th1) cytokines, which tend to be proinflammatory, to Th2 cytokines, which are less proinflammatory (Cantorna, 2006).

Vitamin D also reduces the risk of influenza. There are approximately 200,000 hospitalizations and 36,000 deaths per year from influenza in the United States (Moyad & Robinson, 2008). Cannell and coworkers (2006) suggested that the primary reason influenza has peak incidence rates in winter is that solar UVB doses and, hence, serum 25(OH)D levels are lowest then. This hypothesis was quickly supported by a post hoc analysis of an RCT of vitamin D among African American postmenopausal women living in New York State. Those taking 2,000 IU/day had a 90% reduced incidence of colds and influenza, while those taking 800 IU/day had a 60% reduction (Aloia & Li-Ng, 2007). However, a follow-up study of 2,000 IU/day of vitamin D for 12 weeks failed to find any benefit for upper respiratory tract infections (Li-Ng et al., 2009). Relative humidity and temperature also play important roles in the seasonality of influenza (Shaman, Pitzer, Viboud, Lipsitch, & Grenfell, 2010).

Investigators conducting an ecological study reported that the case-fatality rate during the 1918–1919 A/H1N1 pandemic influenza in the United States was inversely correlated with solar UVB indices. The data used in this study were obtained by the U.S. Public Health Service surveys in 12 communities (Britten, 1932). The summertime solar UVB index explained 52% of the variance, while the wintertime solar UVB index explained 46% of the variance (Grant & Giovannucci, 2009). The mechanisms proposed were reduced risk of the cytokine storm as a result of the $1,25(OH)_2D$-induced shift of cytokine production away from proinflammatory factors and the induction of cathelicidin (and defensins) to reduce the risk of bacterial pneumonia. The current swine flu is also A/H1N1 and there is good evidence that the hardest hit people are those in groups that are known to be vitamin D deficient: pregnant women (Mangtani, Mak, & Pfeifer, 2009), Australian Aborigines, the obese, and so on.

Vitamin D is also beneficial in reducing the risk of severe sepsis, which had incidence rates of about 135 per 100,000 and mortality rates or 38 per 100,000 in 2003 (Dombrovskiy, Martin, Sunderram, & Paz, 2007). In a review of the epidemiology of septicemia in the United States, I (WBG) pointed out that the general geographical features of these rates—such as the highest incidence occurring in the northeast and the lowest in the west, seasonal rates being highest in winter and lowest in summer, and the highest prevalence being among African Americans—were consistent with a vitamin D-sensitive disease (Grant, 2009e). This hypothesis was quickly supported by a study of patients in an intensive care unit in Atlanta, Georgia with the finding that those in the intensive care unit with sepsis had very low serum 25(OH)D levels (Jeng et al., 2009).

Interest in the role of vitamin D in the innate immune system is increasing rapidly and has been reviewed in several recent articles (Adams, Liu, Chun, Modlin, & Hewison, 2007; Bikle, 2008; White, 2008). Reports from RCTs underway will strengthen the link between higher serum 25(OH)D levels and reduced risk of several infectious diseases such as influenza (Urashima et al., 2010).

Neurological Diseases

In 2002, the prevalence of dementia in the United States among individuals aged 71 and older was 13.9%, comprising about 3.4 million individuals. The corresponding values for Alzheimer's disease (AD) were 9.7% and 2.4 million individuals (Plassman et al., 2007). Evidence is mounting that vitamin D protects against cognitive impairment and dementia. Authors of one review pointed out that since every cell in the body, including in the brain, has VDRs, vitamin D likely serves an important role in protection of the brain (McCann & Ames, 2008). Subsequently, a review of the neuroprotective properties of vitamin D was published (Buell & Dawson-Hughes, 2008). Several studies have reported a correlation between serum 25(OH)D and cognitive function (Buell et al., 2009; Llewellyn, Langa, & Lang, 2009; Wilkins, Birge, Sheline, & Morris, 2009). Based on these reports and the fact that many vitamin D-sensitive diseases either precede or accompany dementia, I (WBG) have previously suggested that vitamin D likely reduces the risk of dementia (Grant, 2009b). In a cross-sectional investigation of 25(OH)D, dementia, and magnetic resonance imaging (MRI) measures of CVD in 318 elders receiving home care (aged 65–99 years) from 2003 to 2007, 25(OH)D insufficiency ($\leq$ 20 ng/ml) was associated with more than twice the risk of all-cause dementia (OR = 2.3, 95% CI [1.2, 4.2]), AD (OR = 2.5, 95% CI [1.1, 6.1]), and stroke (with and without dementia symptoms; OR = 2.0, 95% CI [1.0, 4.0]; Buell et al., 2010). In a recent historical cohort study involving 5,396 persons with AD (61.7% women) with mean age 76.9 years compared to a similar cohort without AD, those with AD were found to have incidence rates for vitamin D-sensitive diseases

that were 1.3 times (malignancy) to 3.1 times (cerebrovascular disease) greater than those without AD (Malone et al., 2009). This finding adds additional support to the hypothesis that those with AD are likely to be vitamin D deficient, though whether the AD is a result of D deficiency or causal for deficiency remains to be determined.

Pregnancy Outcomes

Vitamin D is especially important during pregnancy and lactation, and the amount of vitamin D required daily is much higher than during other periods of life. Bruce Hollis of the Medical University of South Carolina has been studying the requirements as well as conducting an RCT of vitamin D supplementation during pregnancy and lactation (Hollis, 2007). In the first results reported from this study, 130 Black, White, and Hispanic women were given 400, 2,000, or 6,000 IU/day of vitamin D3 or a placebo starting at the 12th week of pregnancy. Hollis found that 2,000 IU/day was insufficient to raise the infants' serum 25(OH)D level above 20 ng/ml, while 6,000 IU/day was sufficient, and there were no adverse metabolic events such as hypercalcemia or hypercalcuria (Hollis & Wagner, 2009). The author suggested that the higher doses were associated with better neonatal outcomes.

Seasonal birth rates for mental disorders diagnosed later in life (adjusted for overall birth rates) are highest in spring (Torrey, Miller, Rawlings, & Yolken, 1997), which could reflect vitamin D inadequacies during the later stages of pregnancy, increases in infectious diseases in winter or both. Higher vitamin D provision in humans seems to reduce the risk of such effects, possibly by reducing risk of maternal infections, especially viral infections (Acs, Bánhidy, Puhó, & Czeizel, 2005; McGrath, Eyles, Mowry, Yolken, & Buka, 2003). An adverse effect of infection during pregnancy is increased body temperature. As Edwards wrote, "In experimental animals the most common defects associated with maternal hyperthermia are of the neural tube, with microphthalmia, cataract and microcephaly and associated functional and behavioral problems; defects of craniofacial development including clefts are also seen. Defects in the axial and appendicular skeleton and in the body wall, teeth, and heart are also commonly found. Nearly all these defects have been found in human epidemiological studies following maternal fever or hyperthermia during pregnancy" (Edwards, 2007).

Vitamin D has been reported to reduce the risk of preeclampsia in two studies. In the United States, a 20 ng/ml or lower 25(OH)D concentration doubled the risk of preeclampsia (adjusted OR = 2.4; 95% CI [1.1, 5.4]; Bodnar, Catov, et al., 2007), while in Norway the OR for preeclampsia for women with a total vitamin D intake of 600–800 IU/day compared with an intake of <200 IU/day was 0.76 (95% CI [0.60, 0.95]; Haugen et al., 2009).

Vitamin D in Infancy and Childhood

Higher serum 25(OH)D concentrations in infancy appear to reduce the risk of developing type 1 diabetes mellitus (T1DM), respiratory infections, and asthma. In Finland during a period ending in 1964, infants were supplemented routinely with 2,000 IU/day of vitamin D. Later investigation found that such supplementation was associated with reduced risk of T1DM of ~80% over follow-up to the age of 30 years (Hypponen, Laara, Reunanen, Jarvelin, & Virtanen, 2001). Since then, the vitamin D supplementation level has dropped to 400 IU/day and the incidence of T1DM in Finland has climbed steadily (Harjutsalo, Sjoberg, & Tuomilehto, 2008); whether this increase might reflect altered viral infection rates or other lifestyle factors in not known. Other recent articles have supported the role of vitamin D in reducing the risk of T1DM (Mohr et al., 2008). T1DM follows autoimmune damage to pancreatic islets with loss of beta cells and has many environmental triggers, both known (including certain viral infections and chemical insults) and unknown. Other hypotheses to explain risk of T1DM in Finland, such as early weaning and early introduction of cow's milk, have been evaluated and found wanting (Savilahti & Saarinen, 2009).

Infants are susceptible to respiratory infections such as influenza, respiratory syncytial virus (RSV; Hall et al., 2009), and invasive pneumococcal disease (Ampofo et al., 2008). Vitamin D reduces the risk of influenza (Aloia & Li-Ng, 2007; Cannell, Zasloff, Garland, Scragg, & Giovannucci, 2008), and the incidence of RSV has been found to be inversely correlated with solar UVB dosages (Yusuf et al., 2007). In a study in Utah, the incidence of invasive pneumococcal disease within 2 weeks of an influenza illness and within 4 weeks of RSV infections was shown to have strong inverse correlations with UVB availability (Ampofo et al., 2008). I (WBG) also suggested in an earlier article that skin pigmentation affects the risk for RSV infection in Hawaii through effects on vitamin D production (Grant, 2008b) on the basis of data showing that those with darker skin generally had higher infection rates (Yorita et al., 2007).

There is increasing evidence that asthma is an autoimmune disease linked to infections early in life and that higher serum 25(OH)D concentrations, especially in utero or in infancy, appear to reduce the risk of developing asthma (Ginde, Mansbach, & Camargo, 2009); for example, an inverse correlation between maternal serum 25(OH)D concentrations and asthma at age 5 years has been found in Finland (Erkkola et al., 2009).

Since the noncalcemic health benefits of vitamin D have been realized only recently, it is very likely that additional health benefits will be found for higher serum 25(OH)D levels in infancy and early childhood like, for example, the increase in bone strength in offspring aged 9 years found with better maternal repletion (Javaid et al., 2006).

Mortality Rates

Several studies have reported that increases in oral vitamin D intake or higher serum 25(OH)D concentrations are associated with lower mortality rates. A meta-analysis of vitamin D supplementation found that relative risk for mortality from any cause was 0.93 (95% CI [0.87, 0.99]) for a mean oral intake of 528 IU/day of vitamin D over 5.7 years (Autier & Gandini, 2007).

In a cross-sectional study of 3,400 seniors in the United States followed up for a median time of 7.3 years, adjusting for demographics, season, and cardiovascular risk factors, baseline 25(OH)D concentrations were inversely correlated with all-cause mortality risk (adjusted HR = 0.95, 95% CI [0.92, 0.98], per 4 ng/ml 25[OH]D; Ginde, Scragg, et al., 2009). Other recent articles (Dobnig et al., 2008; Melamed et al., 2008; Semba et al., 2009) reported similar findings. In a preliminary meta-analysis, the serum 25(OH)D dose–mortality rate relation was found to be similar to the relations between serum 25(OH)D and rates for breast and colorectal cancer and CVD.

Racial Disparities

African Americans generally have poorer health, more disease, and shorter life expectancies than White, Hispanic, and Asian Americans. Several factors contribute to these disparities, three of which we focus on here. The first is socioeconomic status (Satcher & Higginbotham, 2008; Woolf, Johnson, Fryer, Rust, & Satcher, 2008), itself strongly linked to increased rates of obesity due to the fact that energy-dense, nutrient-poor foods are heavily subsidized in the United States (Dammann & Smith, 2009). The second factor is that African Americans have a higher prevalence of the apolipoprotein-E (ApoE) epsilon4 (ApoE4) allele than White Americans at ~29% and 12%, respectively (Borenstein et al., 2006). ApoE4 is a risk factor for the metabolic syndrome and obesity (Sima, Iordan, & Stancu, 2007), AD (Roses, 2006), coronary heart disease (Singh, Singh, Bhatnagar, Kaur, & Gaur, 2008), and, likely, prostate cancer (Grant, 2010b) and is associated with lower life expectancy (Ewbank, 2007). The third factor is the lower serum 25(OH)D concentrations seen in African Americans due to darker skin pigmentation (Harris, 2006); mean serum 25(OH)D concentrations are ~15 ng/ml in African Americans compared to ~26 ng/ml in White Americans (Ginde, Scragg, et al., 2009; Looker et al., 2008). A few studies have reported disease rates in relation to serum 25(OH)D values in African Americans, for example, for cancer (Giovannucci, Liu, & Willett, 2006; Grant, 2006, 2008a), cognitive impairment (Wilkins et al., 2009), and peripheral arterial disease (Reis, Michos, von Muhlen, & Miller, 2008). Of the three major health risk factors discussed above, vitamin D deficiency would be the easiest to remedy and also the most cost effective. Bibuld (2009) and Grant and Peiris (2010) discuss the benefit of higher serum 25(OH)D levels for African Americans in two recent reviews.

A recent example underscores the likely role of low vitamin D levels among African Americans in higher disease rates. When all costs including morbidity and mortality are included, the per capita cost of smoking for African Americans in California is 30% higher than for all Californians (Max, Sung, Tucker, & Stark, 2010). The diseases associated with smoking are cancers, CVD, and respiratory diseases, all of which are among those increased with hypovitaminosis D.

Recommendations

The health benefits of vitamin D are legion and the risks of adequate supplementation are few. The well-documented benefits for the health of the locomotor system of adequate vitamin D repletion are clear reasons for increasing serum 25(OH)D concentrations so as to at least avoid deficiency at every stage of life; the other associated effects can be regarded as likely incidental benefits. The primary concern about supplemental vitamin D is the risk of causing hypercalcemia in those with granulomatous diseases such as sarcoidosis (Hewison et al., 2007), in a small fraction of those with lymphoma (Seymour, Gagel, Hagemeister, Dimopoulos, & Cabanillas, 1994), and in undiagnosed primary hyperparathyroidism. Because whole-body exposure to the sun can generate 10,000 IU of vitamin D in a few minutes to a few hours depending primarily on the solar elevation angle, elevation or altitude, and cloud cover (Webb & Engelsen, 2006) as well as skin color, it is logical that there are few, if any, adverse effects at such physiological doses (Hathcock, Shao, Vieth, & Heaney, 2007). The solar elevation angle is important since, at lower values, there is greater attenuation from ozone and molecular scatter. The solar elevation angle should be greater than 45° for efficient vitamin D production.

It has been found that the human body can use 3,600 IU/day of vitamin D (Heaney, Davies, Chen, Holick, & Barger-Lux, 2003). Other authors have suggested that optimal serum 25(OH)D concentrations are 30–60 ng/ml (100–150 nmol/l; Cannell, Hollis, et al., 2008; C. F. Garland, Grant, Mohr, Gorham, & Garland, 2007; Gorham et al., 2007; Hypponen, Boucher, Berry, & Power, 2008) based on maximal reduction in adverse features associated with poor vitamin D repletion. Since it requires intakes of ~1,000 IU/day to increase serum 25(OH)D by 6–10 ng/ml (Heaney, Davies, Chen, Holick, & Barger-Lux, 2003; Lappe et al., 2007) and this dose has been shown to improve bone strength and reduce fracture rates in osteoporosis, this would be a reasonable daily dose for adult women to take fall to spring. In summer, casual UVB irradiance can increase serum 25(OH)D by 10–15 ng/ml (Grant, 2006; Hypponen & Power, 2007), and therefore oral intake could be reduced in summer unless lifestyle factors preclude regular outdoor activity. However, production of 25(OH)D from solar UVB decreases by up to a factor of 4 for those over the age of 60 years compared to those under the age of 20 years (MacLaughlin & Holick, 1985), so intakes of 1,000–2,000 IU/day all year round are, therefore, advisable for most people. Those with higher body mass index have been found to have lower serum 25(OH)D levels (Lagunova, Porojnicu, Lindberg, Hexeberg, & Moan, 2009) and, since vitamin D is lost into fat stores (Blum et al., 2008), it is probable that vitamin D intakes should be based on body weight. Similarly, as for other forms of medication and supplementation, vitamin D dosages for supplementation throughout the growing period require formal assessment.

Estimates of the health benefits of increasing serum 25(OH)D levels at the population level from 20–25 ng/ml to

40–45 ng/ml have been made for Western Europe (Grant, Cross et al., 2009), the United States (Grant, 2009d), Canada (Grant, Schwalfenberg, Genuis, & Whiting, 2010), the Netherlands (Grant & Schuitmaker, 2010), and Nordic countries (Grant, Juzeniene, & Moan, 2010). The potential reduction in mortality rate was estimated to be 15–20%, corresponding to a 2-year increase in life expectancy, while the economic burden of disease should be reduced by 10–15%.

Summary and Conclusion

The health benefits of vitamin D have been reported for a number of chronic and infectious diseases, based largely on ecological, cross-sectional, and observational studies with a few well-conducted RCTs in support. The strongest evidence is for bone diseases, many types of cancer, CVD, metabolic diseases such as diabetes mellitus, multiple sclerosis, cognitive impairment, and some infections such as influenza, pneumonia, and septicemia. Weaker evidence exists for diseases such as asthma. Recent studies have also found that pregnancy outcomes are improved with higher serum 25(OH)D levels. Raising serum 25(OH)D levels to above 40 ng/ml from a level in the low-to-mid 20s seems to reduce the risk of mortality by about 15% and increase life expectancy by about 2 years.

Additional RCTs are sorely needed to provide incontrovertible evidence as to whether vitamin D has the health benefits expected from available epidemiological studies, both cross-sectional and prospective. However, moving forward with recommendations for higher intakes or better skin production of vitamin D to eliminate vitamin D deficiency should not be delayed while such studies are proceeding. Furthermore, the track record of modest supplementation for maintenance of bone health is incontrovertible. The Institute of Medicine of the National Academies has convened an 14-member committee addressing the Dietary Reference Intakes for Vitamin D and Calcium. Their report was released on November 30, 2010. For vitamin D, the estimated average requirement for all ages was 400 IU/d, recommended dietary allowance 600 IU/d, and upper level intake varying from 1000 IU/d for infants 0 to 6 months to 4000 IU/d for those over the age of nine years. (IOM, 2010)

Declaration of Conflicting Interests

The author(s) declared a potential conflict of interest (e.g. a financial relationship with the commercial organizations or products discussed in this article) as follows: William B. Grant receives or has received funding from the UV Foundation (McLean, Virginia), the Vitamin D Society (Canada), the Sunlight Research Forum (Veldhoven), Bio-Tech-Pharmacal (Fayetteville, Arkansas), and the Vitamin D Council (San Luis Obispo). Barbara J. Boucher has no conflicts of interest to report.

Funding

The author(s) received no financial support for the research and/or authorship of this article.

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