5-2011

Vitamin D Healthy Bones and Beyond

Mary C. Nolan
St. Catherine University

Vitamin D

Healthy Bones and Beyond

Mary C. Nolan

St. Catherine University

May 5, 2011

Abstract

The past decade has sparked renewed interest in vitamin D. This interest is at the forefront of research and debate. Hardly a day goes by when information regarding the vitamin is not in the health care news, highlighting new data suggesting health benefits that extend beyond healthy bones. Accompanying this renewed interest has been a proliferation of published studies related to adverse consequences of deficiency for a broad range of chronic illnesses. This paper presents research demonstrating the basics of vitamin D, effects vitamin D has on diverse body systems, various position statements from national health organizations on the significance of the research, opinions from expert researchers, debates among health care professionals, and updated guidelines from the Institute of Medicine regarding recommended daily allowances.

Intriguing findings from recent research have led to increased interest in vitamin D among health care providers, researchers, and the general public. These findings include concern about possible widespread deficiency in the general population, calls for supplementation, and use of large doses of vitamin D as treatments for a variety of conditions (Brannon, Yetley, Bailey, & Picciano, 2008). Vitamin D antirachitic properties are generally well recognized and the role in calcium and phosphorus homeostasis is established. The discovery that many tissues and cells in the body have a vitamin D receptor and that several possess the enzymatic machinery to convert the primary circulating form to the active form has provided new insight into the function of this vitamin. Except for effects on bone health, which are strongly supported in randomized clinical trials (RCTs), the evidence for most of the other potential benefits is generally considered to be less definitive (Brannon, et al., 2008).

Critically evaluating the evidence regarding the possible benefits of vitamin D on a multitude of health outcomes is difficult. The bulk of current data is based on observational, epidemiological studies which are useful for generating hypotheses but not for proving causality. Many studies have failed to control factors that confuse study findings, such as diet, baseline vitamin D status, and physical activity. Few of the observational associations have been confirmed by RCTs and a majority of the interventional studies include calcium supplementation (Thacher & Clarke, 2011).

Nurse practitioners, as primary care providers, need to be acquainted with evidence based research involving vitamin D in order to answer their patients' questions and concerns as they seek to understand the significance vitamin D has on their health and well-being.

Historical Perspective

The road to discovery of vitamin D began with recognition of the childhood bone disease called rickets. The first formal medical treatise on rickets was published by Francis Glisson in 1650, when it was identified as a new disease that resulted in severe growth retardation and bony deformities in children. During the industrial revolution of the 1800's, the prevalence of rickets increased dramatically, ranging from 40% to 60% among children in crowded and polluted urban areas who lacked adequate sun exposure. In 1822, Sniadecki was the first to recognize and report the association of rickets with a lack of sunlight exposure. By the mid 1800's cod liver oil had been established as an effective treatment for rickets. The work of Mellanby and McCollum led to the discovery of vitamin D as the agent in cod liver oil that had antirachitic properties. This discovery eventually led to the fortification of milk and other foods with vitamin D in the 1930's, and as a result rickets all but disappeared in North America and Europe (Thacher & Clarke, 2011). In the early 1950's there was an outbreak of hypercalcemia which was thought to be due to the over fortification of milk, and as a result, most European countries forbid further fortification (Holick, 2009).

Definition of Vitamin D Deficiency, Insufficiency, and Toxicity

Although there is no consensus from the scientific community on optimal levels of 25-hydroxyvitamin D as measured in serum, vitamin D deficiency is defined by most experts as a serum 25-hydroxyvitamin D level of <20ng/mL. Vitamin D insufficiency is defined as a serum 25-hydroxyvitamin D level of 21-29ng/mL. Vitamin D toxicity is defined as a serum 25-hydroxyvitamin D level >150ng/mL and is associated with hypercalcemia, hypercalciuria, and

often hyperphosphatemia. The preferred sufficiency level for 25-hydroxyvitamin D is recommended to be >30ng/mL (Holick, 2009).

Incidence of Deficiency, Insufficiency, and Toxicity

The Centers for Disease Control and Prevention (CDC) has reported the percentage of adults achieving vitamin D sufficiency has declined from about 60% in 1994-1998 to approximately 30% in 2001-2004 in Caucasians, and from about 10% to approximately 5% in African Americans during the same time period. Furthermore, more people have been found to have severe deficiency with a level <10ng/mL. Even when using a conservative definition of deficiency, many people routinely seen in clinical practice will be deficient in vitamin D (Kennel, Drake, & Hurley, 2010).

Toxicity is extremely rare and generally occurs after ingestions of large doses of vitamin D (>10,000 IU/d) for prolonged periods in people with normal intestinal absorption, or in people who may be concurrently ingesting generous, if not excessive, amounts of calcium (Kennel et al., 2010). Toxicity from sunlight is not possible. When approximately 20,000 units have been made, the same ultraviolet light that created vitamin D begins to degrade it. A steady state is reached that prevents the skin from converting too much vitamin D; there are no reports on toxicity from exposure to the sun (Hollick, 2007).

Deficiency and insufficiency are becoming more common in the U.S. as well as globally because of decreased sunlight exposure, increased use of sunscreens, limited dietary sources, risk factors which interfere with absorption in the gut, cultural dress, habits, seasons, latitude, hepatic and renal disease (Kennel et al., 2010).

Vitamin D Metabolism and Physiology

During the past decade important advances in the study of vitamin D have been made. New investigations into the effects have generated some significant changes in the understanding of the metabolism and the extent of the roles vitamin D plays in the endocrine and autocrine pathways. To understand the endocrine and autocrine pathways it is important to be familiar with the two bioequivalent forms of the vitamin. Vitamin D2, also known as ergocalciferol, is obtained from dietary vegetable sources and is produced commercially by irradiation of yeast for food fortification and oral supplements. Vitamin D3, also known as cholecalciferol, is obtained primarily from skin exposure to UVB radiation from sunlight, or from dietary animal sources and oral supplements. Both D2 and D3 can be used in over the counter dietary supplementation (Kulie, Groff, Redmer, Hounshell, & Schrager, 2009).

Cholecalciferol is synthesized from 7-dehydrocholesterol when the skin is exposed to the ultraviolet light from the sun. Both cholecalciferol and ergocalciferol are ingested from the diet, or taken as a dietary supplement. The vitamin D binding protein transports cholecalciferol and ergocalciferol to the liver where it undergoes hydroxylation to calcidiol (25-hydroxyvitamin D), the primary circulating form of vitamin D. The half-life of 25-hydroxyvitamin D in the liver is approximately 3 weeks, which underscores the need for frequent replenishment (Cronin, 2010).

After undergoing hydroxylation in the liver, 25-hydroxyvitamin D is transported to the kidneys where it is hydroxylated by the enzyme 1 alpha-hydroxylase to calcitriol (1,25-dihyroxyvitamin D), the physiologically active or hormonal metabolite. Renal production of 1,25-dihydroxyvitamin D is tightly regulated by plasma parathyroid hormone (PTH), serum calcium, and phosphorus levels. The role of 1,25-dihydroxyvitamin D in the endocrine system is to promote mineralization of new bone, and the action is coordinated to increase both calcium

and phosphate concentrations in plasma so that these elements can be deposited as new bone mineral (Kulie, et al., 2009).

It is known that the sole active hormonal form, 1,25-dihydroxyvitamin D, acts via a vitamin D receptor (VDR) found on many cells throughout the body. The VDR possesses the enzyme needed to convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. By binding to the VDR, the hormonal form initiates a series of events thought to affect cellular proliferation and differentiation, inflammation, the immune, endocrine and rennin-angiotension systems, calcium and phosphorus homeostasis, insulin resistance, and lipid metabolism. Over thirty-seven tissues are now known to possess the VDR site. These tissues are found in five physiologic systems: the immune, pancreas, cardiovascular, muscle, and central nervous systems. The impact of low circulating levels of 1,25-dihydroxyvitamin is thought to be associated with various disease states due to the cell-differentiating or antiproliferative influence. All of the health benefits of vitamin D discovered in the last ten years are from the hormonal action and this is causing all the excitement in the medical community (Thacher & Clarke, 2010). In addition to the important role of skeletal development and maintenance, scientific interest lays in the roles vitamin D plays when binding to the VDR (Cronin, 2010).

How vitamin D is Measured

Serum 25-hydroxyvitamin D is the most commonly accepted measure of vitamin D adequacy, because it is the major circulating form of vitamin D, it reflects cutaneous and dietary contributions and it has a fairly long circulating half-life of 15 days. However, the serum 25-hydroxyvitamin D level does not reveal the amount stored in body tissues (Kennel et al., 2010).

Food Sources of Vitamin D

Very few foods in nature contain vitamin D. The flesh of fatty fish (such as salmon, tuna, and mackerel) and fish liver oils are among the best sources. Small amounts of vitamin D are found in beef liver, cheese, and egg yolks. Vitamin D in these foods is primarily in the form of vitamin D_3. Some mushrooms provide vitamin D_2 in variable amounts.

Fortified foods provide most of the vitamin D in the American diet. For example, almost all of the U.S. milk supply is voluntarily fortified with 100 IU/cup. Other dairy products made from milk, such as cheese and ice cream, are generally not fortified. Ready-to-eat breakfast cereals often contain added vitamin D, as do some brands of orange juice, yogurt, margarine and other food products. Following is a table listing several food sources with their international units (IU) per serving and per cent (%) of the daily value listed.

Several food sources of vitamin D are listed in Table 1

Table 1
Selected Food Sources of Vitamin D

Food	IUs per serving*	Percent DV**
Cod liver oil, 1 tablespoon	1,360	340
Salmon (sockeye), cooked, 3 ounces	447	112
Mackerel, cooked, 3 ounces	388	97
Tuna fish, canned in water, drained, 3 ounces	154	39
Milk, nonfat, reduced fat, and whole, vitamin D-fortified, 1 cup	115-124	29-31
Orange juice fortified with vitamin D, 1 cup (check product labels, as amount of added vitamin D varies)	100	25
Yogurt, fortified with 20% of the DV for vitamin D, 6 ounces (more heavily fortified yogurts provide more of the DV)	80	20
Margarine, fortified, 1 tablespoon	60	15
Liver, beef, cooked, 3.5 ounces	49	12
Sardines, canned in oil, drained, 2 sardines	46	12
Egg, 1 large (vitamin D is found in yolk)	41	10
Ready-to-eat cereal, fortified with 10% of the DV for vitamin D, 0.75-1 cup (more heavily fortified cereals might provide more of the DV)	40	10
Cheese, Swiss, 1 ounce	6	2

* IUs = International Units. ** DV = Daily Value. DVs were developed by the U.S. Food and Drug Administration to help consumers compare the nutrient contents among products within the context of a total daily diet. The DV for vitamin D is currently set at 600 IU for adults less than 70 years old and 800 IU for adults over 70 years old. Food labels, however, are not required to list vitamin D content unless a food has been fortified with this nutrient. Foods providing 20% or more of the DV are considered to be high sources of a nutrient, but foods providing lower percentages of the DV also contribute to a healthful diet.
Source: *National Institute of Health, Office of Dietary Supplements (2011)*

Recommended Dietary Allowances

In November 2010 the Institute of Medicine (IOM) revised the recommended dietary allowance (RDA) for vitamin D intake. The RDA values represent the minimum amount of a vitamin needed to prevent a deficiency in a healthy adult. The RDAs are revised periodically to reflect the latest scientific research. This was the first update since 1997. A newer standard, the Dietary Reference Intake (DRI), is sometimes used to represent the optimal level of nutrient needed to ensure wellness (Institute of Medicine (IOM, 2010).

The revised guidelines pertain only to the well-established role of vitamin D in bone health and fracture reduction. The IOM committee reported an exhaustive review of studies of potential health outcomes was done and the evidence supported a role for the nutrient on bone health but not in other health conditions. Overall, the committee concluded the majority of Americans are receiving adequate amounts of vitamin D. Furthermore, the committee found emerging evidence that too much may be harmful. The report felt the evidence for all other benefits was “inconsistent and /or inconclusive or did not demonstrate causality” Following is a chart depicting the revised dietary allowances (Institute of Medicine (IOM, 2010).

Estimated Average Requirement (IU/Day)	Recommended Dietary Allowance (IU/Day)	Upper Level Intake (IU/Day)
Ages 9-50 (male & female) (400 IU/Day)	Ages 9-50 (male & female) (600 IU/Day)	Ages 9-50 (male & female) (4,000 IU/Day)
Ages 51-70 (males) (400 IU/Day)	Ages 51-70 (males) (600 IU/Day)	Ages 51-70 (males) (4,000 IU/Day)
Ages 51-70 (females) (400 IU/Day)	Ages 51-70 (females) (600 IU/Day)	Ages 51- 70 (females) (4,000 IU/Day)
Ages 70 and up (male/female) (400 IU/Day)	Ages 70 and up (male/female) (800 IU/Day)	Ages 70 & up (male/female) (4,000 IU/Day)

Source: *Institute of Medicine of the National Academies. November 30, 2010.*

Risk Factors for Vitamin D Deficiency

There are multiple risk factors contributing to vitamin D deficiency. They include age older than 65 years, poor diet, impaired intestinal absorption, obesity, limited/insufficient sunlight exposure, medications that alter metabolism, and renal and hepatic disease (Kennel et al., 2010).

People older than 65 years have decreased 1-alpha hydroxylase activity in the kidneys and decreased synthesis of UVB rays. Insufficient dietary intake conditions include inadequate oral intake, malnutrition, and lactose intolerance. People who are lactose intolerant are at risk because they are unable to drink fortified milk, a major source for vitamin D. Gastrointestinal malabsorption conditions include short bowel syndrome, pancreatitis, inflammatory bowel disease, amyloidois, celiac sprue, and malabsorptive bariatric surgery procedures. Vitamin D requires dietary fat for absorption in the intestine. Conditions that limit fat absorption include crohn's disease, celiac disease, cystic fibrosis, liver disease and surgical removal of part or all of the stomach or intestines. Higher body mass index is associated with lower levels of vitamin D. It is hypothesized that because vitamin D is fat soluble, it is sequestered in fat so there is less available for circulation (Kennel et al., 2010).

Limited/insufficient sunlight exposure also presents as a risk factor. This may be caused by use of sunscreen, the homebound elderly, populations who live in northern latitudes or areas of heavy rain or smog, and cultural or religious reasons where the skin is covered by dress. Anticonvulsants and glucosteroids are strongly associated with increased metabolism of vitamin D which subsequently leads to deficiency (Kennel et al., 2010).

Vitamin D deficiency is also common in the presence of hepatic or renal disease. Severe hepatic disease or failure causes decreased 25-hydroxyvitamin D activity. Renal insufficiency

(identified by a glomerular filtration rate <60%), can cause decreased 1-alpha hydroxylase activity and nephritic syndrome causes decreased levels of vitamin D-binding protein (Kennel et al., 2010).

Individuals of dark-skinned ethnicities are particularly vulnerable. Higher melanin content reduces cutaneous synthesis of vitamin D in response to sunlight. Rickets, the children's disease caused by deficiency is re-emerging as a health care problem in some African American communities. Severe rickets also occurs as part of three rare heritable disorders of vitamin D action (Kennel et al., 2010).

Manifestations of Skeletal Vitamin D Deficiency

Vitamin D deficiency causes bone to demineralize. Adults with osteomalacia may experience comprehensive bone discomfort and muscle aches, often leading to a misdiagnosis of fibromyalgia, chronic fatigue syndrome, or arthritis. Because VDRs are present in skeletal muscle, deficiency may also lead to proximal muscle weakness, increased risk of falls, bone discomfort, (elicited with pressure over the sternum or tibia), and low back pain (in older women). Because the sign and symptoms of deficiency are insidious or nonspecific, it often goes unrecognized and untreated (Bordelon, Ghetu, & Langan, 2009)

Who Should be Screened

Given the multitude of potential adverse health consequences attributed to low vitamin D status, screening for vitamin D deficiency has been advocated but there is not wide-spread consensus. Screening may turn out to be appropriate if it becomes established that a deficiency status contributes in a causal manner to multiple adverse health outcomes. However, in the absence of randomized trials documenting benefit for these varied adverse health outcomes,

population-based screening may be premature. Rather than advocating a population screening approach, it seems prudent to screen people who are identified as high risk, and for whom a prompt musculoskeletal response to optimization of vitamin D status could be expected. Knowledge of the serum 25-hydroxyvitamin D level could help identify the need for therapy and may help to determine an effective dose. Alternatively, empiric supplementation without testing may be justified for patients who have no overt risk factors or evidence of deficiency but are thought to have inadequate sun exposure or dietary intake (Binkley, Ramamurthy, & Krueger, 2010).

Treatment Recommendations for Vitamin D Deficiency

The best cost effective regimen to replenish serum 25-hydroxyvitamin D levels is oral ergocalciferol (vitamin D2) at 50,000 IU per week for eight weeks. Vitamin D2 is the only form available in prescription strength. The optimal time for rechecking the serum levels after repletion has not been clearly defined, but the goal is to achieve a minimum level of 30ng/mL. If values have not reached or exceeded the minimum level, a second eight-week course of ergocalciferol (vitamin D2) should be prescribed. If the serum 25-hydroxyvitamin D levels still have not risen, the most likely cause is non-adherence to therapy or malabsorption. If malabsorption is suspected, consultation with a gastroenterologist should be considered (Bordelon et al., 2009).

After vitamin D levels are replenished a maintenance dosage of cholecalciferol (vitamin D3) should be instituted at 800 to 1,000 IU/day from dietary and supplemental sources (Bordeon, et al., 2009). Cutaneous exposure to sunlight or artificial UVB rays from a tanning bed is also helpful. Exposure to direct sunlight typically of no more than 5-10 minutes on the arms and legs

between the hours of 10am and 3pm during the spring, summer, and fall will prevent vitamin D inadequacy. Exposure to UVB rays either from the sun or from a tanning bed comes with a great deal of controversy (Bordelon et al., 2009).

Literature Review

Calcium plus Vitamin D Supplementation and the Risk of Fractures

The efficacy of calcium with vitamin D supplementation for preventing hip and other fractures in healthy postmenopausal women remains equivocal. A study conducted by Jackson et al., (2006) was initiated that involved 36,282 healthy, postmenopausal women, 50 to 79 years of age, who were already enrolled in a Women's Health Initiative (WHI) clinical trial. The calcium plus vitamin D study was a large-scale, randomized, double-blind, placebo-controlled trial. The trial was designed to test whether calcium and vitamin D supplementation reduced the risk of hip fracture (primary end-point) and all fractures (secondarily end-point) than women assigned to placebo. Participants were randomly assigned to receive 1000mg of elemental calcium as calcium carbonate with 400 IU of vitamin D daily or placebo. Fractures were ascertained for an average follow-up period of 7.0 years.

Hip bone density was 1.06 % higher in the calcium plus vitamin D than in the placebo group ($P<0.01$). Intention- to-treat analysis indicated that participants receiving calcium plus vitamin D supplementation had a hazard ratio of 0.88 for hip fracture, 0.90 for clinical spine fracture, and 0.96 for total fractures. Censoring data from women when they ceased to adhere to the study medication reduced the hazard ratio for hip fracture to 0.71. Effects did not vary significantly according to prerandomization serum vitamin D levels.

The trial demonstrated that calcium with vitamin D supplementation diminished bone loss at the hip, but the observed 12% reduction in the incidence of hip fracture was non-statistically significant. There were no significant reductions in the incidence of clinical vertebral fractures, fractures of the lower arm or wrist, or total fractures. The main adverse effect noted was a small but significant increase in the proportion of women with renal calculi.

Vitamin D Status and the Risk of Cardiovascular Disease Death

VDRs have been found on cardiomyocytes and vascular endothelial cells, giving the potential to have wide-ranging vascular effects. Evidence from ecologic, animal and clinical studies support a potential beneficial role for vitamin D in the prevention of cardiovascular disease (CVD). Furthermore, vitamin D status has been demonstrated to be associated with several established risk factors for CVD. Epidemiologic evidence, however, is limited and inconclusive; both inverse associations and non associations between vitamin D status and CVD risk have been reported. In addition, vitamin D supplementation had no influence on CVD incidence and mortality in the Women's Health Initiative trial.

In a study of vitamin D status and the risk of CVD death, Kilkkien et al, (2009) investigated whether serum 25-hydroxyvitaimin level predicted mortality from CVD. The study was based on the Mini-Finland Health Survey and included 6,219 men and women with a minimum age of 30 years who were free from CVD at baseline (1978-1980). During follow-up through 2006, 640 coronary disease deaths and 293 cerebrovascular disease deaths were identified. Cox's proportional hazard model was used to assess the association between 25-hydrxyvitamin D and risk of CVD death. Levels of 25-hydroxyvitamin D were determined from serum collected at baseline. This cohort study provided evidence that a low circulating level of

vitamin D may predict a higher risk of CVD death. The observed association was particularly striking for mortality from cerebrovascular disease; subjects in the highest quartile of serum 24-hydroxyvitamin level had less than half the risk of cerebrovascular death as those in the lowest quartile.

The main strengths of the study lay in the prospective design and the fairly large national representative population sample. A further strength of the study was the information on CVD and the risk factors at baseline from the physician's examinations. While the detailed data on multiple CVD risk factors allowed adjustment for potential confounders, the possibility of residual confounding could not be ruled out. It could be speculated that persons with chronic illness may have reduced serum vitamin D levels because of their limited exposure to sunlight and inadequate dietary intake. This raises the possibility that low vitamin D status is only a nonspecific indicator of chronic illness rather than a direct contributor to disease pathogenesis (Kilkkien et al., 2009).

Calcium plus Vitamin D supplementation and the Risk of Colorectal Cancer

As the second leading cause of death from cancer in the U.S. colorectal cancer is the focus of considerable preventive effort. Most observational studies have associated increased calcium and vitamin D intake with a decreased risk of colorectal cancer and recurrent polyps.

As part of the Women's Health Imitative (WHI), Wactawski-Wende, et al. (2006) conducted a clinical trial to determine whether calcium plus vitamin D supplementation would help prevent colorectal cancer. A total of 36,282 postmenopausal women, ages 50 to 79 years were enrolled. The study was a randomized double-blind, placebo-controlled trial. 18,176 women received 500mg of elemental calcium as calcium carbonate with 200 IU of vitamin D3

twice daily and 18,106 received a matching placebo for an average of 7.0 years. Baseline levels of serum 25-hydroxyvitamin D was assessed in a nested case-control study.

The strengths of the study included the randomized, double-blind, placebo-controlled design; the large racial and ethnically diverse study population; the comprehensive assessment of risk factors for colorectal cancer at baseline; and the standardized assessment of colorectal-cancer events in a blinded fashion.

The incidence of invasive colorectal cancer did not differ significantly between women assigned to calcium plus vitamin D supplementation and those assigned to placebo and the tumor characteristics were similar in the two groups. The frequency of colorectal-cancer screening and abdominal symptoms was similar in the two groups. There were no significant treatment interactions with baseline characteristics. The conclusion of the study showed daily supplementation of calcium with vitamin D for seven years had no effect on the incidence of colorectal cancer among postmenopausal women in a randomized trial. The long latency associated with the development of colorectal cancer, along with the seven-year duration of the trial, may have contributed to this null finding. Ongoing follow-up will assess the longer-term effect of this intervention. The results do not provide support for the general use of calcium plus vitamin D supplementation to prevent colorectal cancer.

Vitamin D Supplementation and Total Mortality

In a meta-analysis of eighteen independent randomized controlled trials, Autier and Gandini (2007) found an intake of ordinary doses of vitamin D supplements was associated with decreases in total mortality rates. The study design was the quantitative synthesis of randomized controlled trials that could contribute to evaluating the impact of vitamin D supplementation on

death from any cause. The trials included 57,311 participants. In the meta-analysis, the risk of dying from any cause in subjects who participated in randomized trials testing the impact of vitamin D supplementation on any health condition. A total of 4,777 deaths from any cause occurred during a trial size-adjusted mean of 5.7 years. The trail size-adjusted mean daily vitamin D dose was 528 IU.

In the meta-analysis, data related to groups receiving calcium and vitamin D supplementation and vitamin D supplementation alone were considered the intervention group and calcium supplementation without vitamin D or with placebo were considered the control group. The summary relative risk did not change according to the addition of calcium supplements in the intervention. There was a substantial increase from baseline levels of serum 25-hydroxyvitamin D in the intervention groups, while levels tended to decrease in control groups. This translated to a 1.4 to 5.2 fold difference in serum hydroxyvitamin D level between intervention and control groups. However, increases from baseline levels and in-study differences between intervention and control groups seemed unrelated to daily dose taken.

In conclusion, the intake of ordinary doses of vitamin D supplements seems to be associated with decreases in total mortality rates. The relationship between baseline vitamin D status, dose of vitamin D supplements, and total mortality rates remains to be investigated. Population-based, placebo-controlled randomized trial with total mortality as the main end point should be organized for confirming these findings (Autier & Gandini, 2007).

Dr. JoAnn Manson, chief of preventive medicine at Brigham and Women's Hospital, points out that nearly all of the proliferating studies involving vitamin D are observational, comparing people with high and low levels of vitamin D and correlating those levels with

whether or not the person has the disease. Dr. Manson goes on to point out these studies have the potential for error. People with higher vitamin D levels may be healthier because they exercise more, eat healthier, and have more sun exposure. Those who are sick may have low levels because they do not have those healthy habits.

The large-scale randomized clinical trials showing benefits in terms of prevention of cardiovascular disease, diabetes, cancer, hypertension, cognitive decline, depression, and autoimmune disease have not been initiated.

Future clinical trials, including a National Institutes of Health-funded 5-year 20,000-participant prospective RCT comparing the effect of supplementation with 2,000 IU/day of vitamin D3 or placebo, will help clarify the benefits and risks of supplementation in many of the disorders discussed above (Thacher & Clarke, 2011).

Debates/Challenges

Verbiage to Describe Low Vitamin D Status

The terminology used to describe low vitamin D status remains controversial. For example, terminology including deficiency, insufficiency, inadequacy, and hypovitaminosis has been used interchangeably when describing low vitamin D status (Binkley, et al., 2010).

Cutoff Value to Define Deficiency, Insufficiency, and Toxic Levels

Vitamin D deficiency is normally thought of as rickets or osteomalacia. More recently, the term is being associated with other disease outcomes. Reliance on a single cutoff value to define deficiency or insufficiency is problematic because of the wide individual variability of the functional effects of vitamin D and interaction with calcium intakes. Vitamin D toxicity-an

extremely rare event-is unlikely to be caused by prolonged sun exposure or overconsumption of food sources. The most common cause of toxicity is high intake of supplements. The IOM has set the tolerable upper intake level at 4,000 IU but some authorities maintain the upper limit should be raised to 10,000 IU; others argue that there is not enough known about long-term use of such high levels to be able to establish a upper intake level. It appears that concerns about kidney stones and other toxic reactions are largely exaggerated; vitamin D deficiency is the greater threat (Thacher & Clarke, 2011).

Defining Optimal Sufficiency

There is considerable discussion of the serum concentration of 25-hydroxyvitamin D associated with deficiency (e.g., rickets), adequacy for bone health, and optimal overall health. Cut points have not been developed by a scientific consensus process. It is possible that a value for optimal physiologic functioning might differ between individuals. As vitamin D is an endogenously produced hormone, it is not surprising that between-individual variability and regulation would exist. Limited data suggest that variation in vitamin D degradation may exist, in that differences in 25-hydroxyvitamin D capacity between individuals may be based on race. Measurement issues confound data interpretation (Binkley, et al., 2010). An optimal level might depend on the health outcome in question but none of these levels have been established through RCTs (Kennel et al., 2010).

Consensus regarding an optimal concentration continues to evolve; recognizing that controversy exists, there seems to be increasing agreement the values less than approximately 30 to 32 ng/mL indicate less than ideal vitamin D status. These cut point values were suggested based on the long-established role of vitamin D to facilitate calcium and phosphorus absorption

with a deficiency leading to rickets/osteomalcia. In the debate surrounding what value defines optimal status is being confounded by different levels for various tissues end points, that is, the cut point for various nonclassic targets of vitamin D might vary from that for bone (Binkley et al., 2010)

Consistency in Measuring Serum 25-hydroxyvitamin D

Another complication that is open for debate in assessing vitamin D status is the actual measurement of serum concentrations of 25-hydroxyvitamin D. Considerable variability exists among the various assays available and among laboratories that conduct the analyses. This means that compared to the actual concentration of 25-hydroxyvitamin D in a sample of blood serum, falsely low or falsely high value may be obtained depending on the assay or laboratory used. Standard reference materials from the National Institute of Standards and Technology became available in July 2009 that will now permit standardizations of values across laboratories. However, despite assay improvements, health care providers must appreciate that assay variability is present for laboratory results (Binkley et al., 2010)

Defining Who Should be Tested

According to Kennel, et al., 2010) universal screening for vitamin D deficiency is not supported. It is more reasonable to measure people with clinical risk factors for severe deficiency and for those for whom a prompt musculoskeletal response to optimization could be expected. Such screening may in fact be appropriate, if it becomes established that low vitamin D status contributes in a causal manner to multiple adverse health outcomes. However, in the absence of randomized trials documenting benefit for these varied outcomes, population-based screening seems premature. It has been suggested that clinicians should routinely test for hypovitaminosis

D in patients with musculoskeletal symptoms such as bone pain, myalgias, and generalized weakness. These symptoms are often associated with low levels and might be inaccurately diagnosed as fibromyalgia, chronic fatigue, age-related weakness, or even depression (Binkley, et al., 2010). Population reference ranges vary widely depending on ethnic background, age, geographic location, and the sampling season. A person with an optimal level in the summer may become deficient in the winter without any change in diet, but as a result of change in sun exposure (Kennel et al., 2010).

Vitamin D2 versus Vitamin D3

The relative efficacy of D2 vs. D3 continues to be debated. Both forms appear to be effective for preventing or treating disease, provided that an adequate 25-hydrxyvitamin D level is obtained. The variable efficacy may relate primarily to differences in serum half-life and is clinically relevant for dosing and monitoring frequency. Vitamin D3 has the longer half-life and less frequent dosing may be needed (Kennel et al., 2010). Binkley et al. (2010) feels vitamin D3 to be somewhat more potent. It may be possible that this reflects lower affinity of vitamin D2 for vitamin D binding protein in the circulation, leading to more rapid clearance.

Defining Safe Sun Exposure

The greatest debate is over the amount (if any) of sun exposure that might be adequate to produce vitamin D while protecting the skin against skin cancer. Sunlight also plays a role in skin aging, cataracts, and suppression of the immune system (American Cancer Society (ACS, (2004). Dermatologists have been warning the public for years that sunlight, specifically UVA and UVB, is implicated in the causation of the major form of skin cancer, malignant melanoma, as well as other less deadly forms of skin cancer (basal cell and squamous cell). According to

the ACS (2004), the causes of melanoma are still far from being established, and there remain many unanswered questions about the exact relationship of sunlight exposure to the development of skin cancer.

Brightman, Hamann, and Geronemus (2008), purport the benefits of exposure to UVB radiation cannot be separated from the harmful effects. They disagree with the argument for sensible sun exposure, known as intentional UV exposure, as the most cost-effective and efficient method of preventing vitamin D deficiency. Simply put, UV radiation is a carcinogen. With skin cancer comprising half of all cancers in humans, it is estimated the U.S. spends over an estimated $800 million per year managing skin cancers. In addition, the expenditures for treating photoaging (UV induced skin aging) well exceed an estimated $35 billion. Cost, efficiency, morbidity, and mortality are better served by diet and supplement.

The American Academy of Dermatology (AAD) and the AAD Association amended their position statement on vitamin D on December 22, 2010. The AAD recommends that an adequate amount of vitamin D should be obtained from a healthy diet that includes foods naturally rich in vitamin D, fortified foods/beverages, and /or vitamin D supplements. Vitamin D should not be obtained from unprotected exposure to UV radiation. This includes direct exposure from the sun as well as tanning beds.

The ADA report goes on to say that studies have shown that UV radiation from both the sun and tanning devices can cause oncogenic mutations in skin cells. Use of sunbeds has also been associated with increased risk for melanoma and squamous cell carcinoma. There is no scientifically validated, false threshold level of UV exposure from the sun or indoor tanning devices that allows for maximal vitamin D synthesis without increasing skin cancer risk.

Grant, Strange, and Garland (2004) claim the health benefits of UVB seem to outweigh the adverse effects. They conclude there are multiple factors that contribute to skin cancer that include high fat diets and smoking. A better recommendation may be to seek limited but regular solar UVB exposure for vitamin D production and normal seasonal skin accommodation in summer, and avoid sunburns and excessive tanning. They recommend limiting fat consumption and increasing consumption of fruits and vegetables that are rich in antioxidants.

Holick (2007) writes that sensible sun exposure can provide an adequate amount of vitamin D3, which is stored in body fat and released during the winter, when vitamin D cannot be produced. Exposure for 15-20 minutes is equivalent to ingestion of approximately 20,000 IU of vitamin D2. Most tanning beds emit 2-6% UVB radiation and are a recommended source when used in moderation. Further studies are needed to determine optimal vitamin D intake and whether sun-produced vitamin D confers the same health benefits as enhanced doses from oral supplements.

Patient Education

There is considerable education that needs to be done by the nurse practitioner regarding vitamin D in order for the patient to be able to make informed decisions regarding treatment. Before patient education can be started, an extensive history and physical needs to be completed to determine the risk factors for vitamin D deficiency. Current medications, dietary habits, lifestyle (sedentary or active outdoors), BMI, skin color, age, exposure to sunlight, risk factors, family history, past medical history, and acute/chronic health problems (fat malabsorption or kidney disease), lactose intolerance, calculating current vitamin D intake, and daily exposure to sun light need to be scrutinized, evaluated and addressed. Taking a through history determines

the patient risk factors for vitamin D deficiency. Following are educational information to give to patients when counseling.

Nurse Practitioner Counseling

1. Have a baseline 25-hydroxyvitamin D level drawn if known risk factors are present
2. Educate patients on their risk factors on vitamin D deficiency
3. Educate patients on their risk factors for sun exposure
4. Educate patients on the advantages and disadvantages of sun exposure
5. Read food labels to identify foods that naturally have vitamin D
6. Choose foods that naturally have vitamin D or choose fortified foods:
    - Fatty fish
    - Milk (all milk is fortified regardless of fat content/cheese and yogurts generally are not fortified)
    - Choose lactase products if lactose intolerant
    - Majority of ready to eat cereals and some juices are fortified
7. Supplement with 1,000-2,000 IU vitamin D3 daily-year round
8. Provide instructions on maintenance/prevention dosing to avoid recurrent deficiency

Expected Outcomes

- Vitamin D deficiency and insufficiency will be corrected
- Vitamin D deficiency and insufficiency will be prevented
- Healthier population that is vitamin D sufficient
- Disease prevention
- Lower incident of complications from chronic diseases

References

American Academy of Dermatology and AAD Association. (2010). *Position statement on vitamin D*. Retrieved from http://www.aad.org

American Cancer Society (2011) Can melanoma be prevented? Retrieved from http://Cancer.org/Cancer/SkinCancer-Melanoma/OverviewGuide/melanoma-skin-cancer-overview-prevention

Autier, P., & Gandini, S. (2007). Vitamin D supplementation and total mortality. *Archives of Internal Medicine, 167,* 1730-1737. Retrieved from http://www.archinternmed.com

Binkley, N., Ramamurthy, R., & Krueger, D. (2010). Low vitamin d status: definition, prevalence, consequences, and correction. *Endocrinology and Metabolism Clinics of North America, 39,* 287-301.

Bordelon, P., Ghetu, M. V., & Langan, R. (2009). Recognition and management of vitamin D deficiency. *American Family Physician, 80,* 841-846. Retrieved from the American Family Physician Web site at www.aafp.org/afp.

Brannon, P. M., Yetley, E. A., Bailey, R. L., & Picciano, M. F. (2008). Overview of the conference "vitamin D and health in the 21st century: an update. *American journal of Clinical Nutrition, 88, (suppl)*: 483s-90s. Retrieved from http://www.ajcn.org

Brightman, L., Hamann, G., & Geronemus, R. (2008). The vitamin D dilemma. *The Skin Cancer Foundation Journal, XXVI.* Retrieved from http://www.skincancer.org/scf-journal-2008/Print.html

Cronin, S. C. (2010). The dual vitamin D pathways: Considerations for adequate supplementation. *Nephrology Nursing Journal, 37*(1), 19-26, & 36.

Grant, W. B., Strange, R. C., & Garland, C. F. (2004). Sunshine is good medicine. The health benefits of ultraviolet-B induced vitamin D production. *Journal of Cosmetic Dermatology, 2,* 86-98.

Holick, M. F. (2007). Vitamin D deficiency. *New England Journal of Medicine, 357,* 266-281. Retrieved from http://www.nejm.org

Holick, M. F. (2009). Vitamin d status: measurement, interpretation and clinical application. *Annals Epidemiology, 19,* 73-78. doi: 10.1016/j.annepidem.2007.12.001.

Institute of Medicine of the National Academies (2010). *Dietary reference intakes for calcium and vitamin D.* Retrieved from http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for Calcium-and-Vitamin-D

Jackson, R. D., LaCroix, A. Z., Gass, M., Wallace, R. B., Robbins, J., Lewis, C. E.,……..Barad, D. (2006). Calcium plus vitamin D supplementation and the risk of fractures. *New England Journal of Medicine,* 354, 669-683. Retrieved from http://www.nejm.org/doi/full/10.1056/NEJMoa055218?viewType=Print&viewClass=Pri

Kennel, K. A., Drake, M. T., & Hurley, D. L. (2010). Vitamin D deficiency in adults: When to test and how to treat. *Mayo Clinic Proceedings, 85,* 752-758. doi:**10:4065/mcp.2010.0138**

Kilkkinen, A., Knekt, P., Aro, A., Rissanen, H., Marniemi, J., Heliovaara, M., Impivaara, O., & Reunanen, A. (2009). Vitamin D status and the risk of cardiovascular disease death. *American Journal of Epidemiology, 170,* 1032-1039. doi:10.1093/aje/kwp227

Kulie, T., Groff, A., Redmer, J., Hounshell, J., & Schrager, S. (2009). Vitamin D: An evidence-based review. *Journal of the American Board of Family Medicine, 22,* 698-706. doi:10.3122/jabfm.2009.06.090037

Kurt, K. A., Drake, M. T., Hurley, D. L. (2010). Vitamin D deficiency in adults: when to test and how to treat. *Mayo Clinic Proceedings, 85,* 752-758. doi:10.4065/mcp.2010.0138

Thacher, T. D. & Clarke, B. L. (2011). Vitamin D insufficiency. *Mayo Clinic Proceedings, 86,* 50-60. doi:10.4065/mcp.2010.0567

Wende –Wactawski, J., Kotchen, J. M., Anderson, G. L., Assaf, A. R., Brunner, R. L., O'Sullivan, M. J.,……Manson, J. E. (2006). Calcium plus vitamin D supplementation and the risk of colorectal cancer. *New England Journal of Medicine, 354*, 684-696. Retrieved from http://www.nejm.org/doi/full/10.1056/NEJMoa055222?viewType=Print&viewClass=Pri