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A3: Call for education and research into Vitamin D Deficiency/Insufficiency

Introduction

Vitamin D deficiency and insufficiency is being recognized as a major epidemic for both children and adults in the United States.[1] It has been estimated that 30 – 40% of children and 40 – 50% of adults in the United States are at risk of vitamin D deficiency.[2] It has also been estimated worldwide that one billion people are at risk of vitamin D deficiency.[3] Factors such as low sunlight exposure, age-related decreases in vitamin D formation through the skin, and diets low in vitamin D all contribute to the high prevalence of vitamin D deficiency.[4] Vitamin D is a fat-soluble vitamin which is provided either through the diet or by syntheses through exposure to sunlight. The vitamin has two major forms: D2 (or ergocalciferol) and vitamin D3 (or cholecalciferol).[5] The vitamin D produced from its precursor under the skin after exposure to sunlight and/or intake from vitamin D-rich or enriched foods such as wild salmon, milk and orange juice, are typically not enough to maintain adequate levels of vitamin D.[6] The interventions for this widespread public health problem are simple, safe, effective, accessible, and affordable supplemental doses of the vitamin.[7]

Vitamin D Syntheses and Metabolism

Once vitamin D3 is made in the skin, or provided from the diet (as vitamin D2 or D3), it is converted in the liver to 25-hydroxyvitamin D [25(OH)D], which is the major

circulating form of vitamin D.[8] This 25(OH)D is the substrate for production of the active form, 1,25-dihydroxyvitamin D, via two pathways. In the endocrine pathway, 1,25-dihydroxyvitamin D is made in the kidney under tight regulatory control.[3] In the paracrine/autocrine pathway, 1,25-dihydroxyvitamin D is made and used locally by a variety of cells in most tissues of the body, including those of the immune system.[9]

Factors Affecting Vitamin D Deficiency/Insufficiency and Metabolism

One's Vitamin D status depends on several factors.[10] The time of sun exposure, the season, geography, area of skin covered by clothing, and skin pigmentation all can affect how much Vitamin D one's body will produce.[10] Ultraviolet B (UVB) irradiation of the skin for photochemical production of Vitamin D is highest at noon time.[10] Vitamin D levels, i.e. 25-hydroxyvitamin D [25(OH)D] the major circulating form markedly fluctuate with the change of seasons, because the angle of the sun's rays -- which is critical to the amount of UVB radiation reaching the surface of the earth -- changes during the seasons, as well.[10] Maximal Vitamin D production occurs in the summer months, and depending on the latitude, little or no vitamin D may be generated in winter months.[11] In terms of geography, the farther from the equator that one migrates equates to residing at higher latitudes.[12] The higher the latitude that one lives—the less sufficient the ultraviolet radiation from the sun will be for Vitamin D production.[10] Clothing can be a significant factor, as well.[10] Vitamin D deficiency is rampant among women in Saudi

Arabia, despite sunlight exposure, because the traditional clothing nearly completely covers their skin.[10] Skin pigmentation or melanin, is a dominant factor in regulating the production of Vitamin D, under conditions of low sunlight exposure.[11] Melanin acts as a sunscreen, so darker-skinned individuals require at least five times as much sun exposure to form a given amount of Vitamin D versus a very light-skinned person.[10] A person with dark skin (type 5 or 6) requires 10-50 times the exposure to sunlight to produce the same amount of vitamin D3 in their skin as does a lighter-skinned person with skin type 1 or 2.[13] Subsequently, African-Americans have low levels of 25(OH)D in the United States, which typically is more severe the further north one resides.[10]

Sources of Vitamin D

Sun Exposure

As noted above, Vitamin D3 is synthesized in the skin by exposure to direct sunlight (ultraviolet B radiation) and obtained from foods like fish liver oils and cold-water fish.[14] Also, it is found in fortified foods such as milk, breakfast cereals, and juices. Sunscreen use and dark skin pigmentation also reduce skin synthesis of vitamin D.[14] Sunshine is a significant source of vitamin D because UV rays from sunlight trigger vitamin D synthesis in the skin.[15] Once vitamin D is produced in the skin or consumed in food, it requires chemical conversion in the liver and kidney to form 1,25 dihydroxyvitamin D, the physiologically active form of vitamin D.[15]

Dietary Sources

Only a few foods naturally contain vitamin D as ergocalciferol and cholecalciferol.[16] Human breast milk is typically low in vitamin D in temperate climates, containing an average of only 10% of the amount in fortified cow's milk.[14] In the wild, fish are part of a food chain that allows for concentration of vitamin D in the flesh of fatty fish (e.g., salmon, sardines, mackerel), while in lean fish, vitamin D is concentrated in liver (e.g., cod liver oil). Land animals that are exposed to sunlight or have vitamin D in their feed may be a source of vitamin D, but the amount of vitamin D provided in meat is not well documented except for liver. Eggs are a natural source of vitamin D that can be increased when vitamin D is added to chicken feed, but the level is not usually significant. However, eggs processed to remove cholesterol and saturated fat in the USA have a restored vitamin D content of approximately 6% of the Daily Value. Presently, the U.S does not require the vitamin D content of foods on food labels.[17] Fortification of milk and other foods with vitamin D, such as selected cereals, margarines, juices and a few selected brands of cheese, provide the majority (66-84% of the food sources) the vitamin D dietary intake of Americans.[18] Plant foods such as mushrooms which when briefly exposed to UVB produce significant amounts of vitamin[19] and some fortified foods may contain vitamin D2. The biological equivalency of the two forms of vitamin D, ergocalciferol and cholecalciferol in humans, has recently been challenged.[20] Nonetheless, there has been widespread use of vitamin D2 supplements, so there is no doubt that ergocalciferol-based supplements are efficacious. However, continuous use of these supplements, rather than intermittent dosing may be required for efficacious use of vitamin D2.

Supplements

Supplements provide another source of intake. Vitamin D (i.e., cholecalciferol or ergocalciferol) is usually (but not always) found in multivitamin preparations at 10 µg (400 IU) per tablet, with some having only 5 µg (200 IU) but new ones are being introduced with 25 µg (1000 IU). In addition to multivitamins, single vitamin D supplements are largely available as cholecalciferol in 10 µg (400 IU), 25 µg (1000 IU) and 50 µg (2000 IU) dosages. Some calcium supplements contain various amounts of cholecalciferol or ergocalciferol, are in the range 10 to 25 µg (400 -1000 IU) per tablet. These supplements are intended for maintenance of status or for persons who have less than adequate vitamin D intakes. They are not intended for repletion of vitamin D deficiency. For that purpose, higher dosage forms are available through prescription.[4]

Functions of Vitamin D

The most well known biologic function of vitamin D is to maintain normal blood levels of calcium and phosphorus.[15] The 1,25-dihydroxyvitamin D circulates in the blood and acts to promote active calcium and phosphate absorption; working with parathyroid hormone it helps regulate bone metabolism and kidney re-absorption of calcium. By promoting calcium absorption, vitamin D helps to form and maintain strong bones.[15] Additionally, Vitamin D helps with maintaining a healthy immune system, regulation of cell growth and differentiation (thereby exhibiting antitumor activity), and stimulation of insulin production from the pancreas.[4,14] Vitamin D and related analogs are used to treat psoriasis, hypoparathyroidism, renal osteodystrophy, and osteoporosis. Research shows

promise for the use of these agents to treat leukemia, breast, prostate, and colon cancer; and may be efficacious for immunosuppression.[14] Evidence-based research also shows that vitamin D is increasingly recognized as having a role in the health of the cardiovascular system, neurodevelopment, immunomodulation, and regulation of cell growth.[4, 5]

Symptoms and Consequences of Vitamin D Deficiency

It has long been known that vitamin D is crucial for healthy bones. The presence of active vitamin D in the small intestine aids in the absorption of dietary calcium. Individuals with vitamin D deficiency are able to absorb only a third to half as much calcium as those with sufficient levels. Calcium is vital to the mineralization of bone. The two diseases traditionally associated with severe vitamin D deficiency -- rickets in children characterized by deformation or softening of bone and osteomalacia in adults.[21] Chronic vitamin D deficiency is strongly linked to osteoporosis and fractures.[22,23]

Vitamin D deficiency will not only cause rickets in children but also prevent growing children from reaching their maximal genetically determined bone mineral density.[2]

In adults, vitamin D deficiency precipitates and exacerbates osteoporosis and increases the risk of bone fracture.[24] Vitamin D deficiency in adults also causes osteomalacia, which is a painful bone disease that is often misdiagnosed as fibromyalgia or chronic fatigue syndrome.[21]

In addition to the adverse bone health consequences of vitamin D deficiency, it is now recognized that vitamin D deficiency increases risk of many other chronic diseases including deadly cancers of the breast, colon, prostate and esophagus, and other cancers.[13,25-26] Vitamin D deficiency has also been associated with increased risk of type I[27] and type II diabetes,[28,29] multiple sclerosis,[30,31] and rheumatoid arthritis.[32] Hypertension and heart disease have also been recognized to be associated with vitamin D deficiency.[33-36]

Maintaining adequate vitamin D levels (i.e. serum 25-hydroxyvitamin D) has been associated with reducing the risk of developing colon, breast and prostate cancer,[26] decreasing the risk of developing multiple sclerosis[13, 30,31] and type I diabetes.[13] In fact, a growing body of research shows that adequate levels of vitamin D are essential to overall health and well being.[37]

Vitamin D Inadequacy Detection

To identify vitamin D inadequacy, a simple blood test is required for detection of the level of 25(OH)D. Blood testing for vitamin D has only become available in the last 20 years, and has been undergoing refinement since that time.[6] Recent studies have shown that adequate levels of 25(OH)D are in the range of 30 – 100 ng/ml, as opposed to the older standard of below 20 ng/ml defining deficiency.[3] To reflect this adjustment the newer term “insufficiency” is being used to reflect levels lower than 30 ng/ml.

Specifically, insufficiency is defined as vitamin D levels that are equal to or greater than 20ng/ml but lower than 30 ng/ml.[38,39] For neonates, there is liquid Vitamin D, and for children and adults there is a tablet form that is easily tolerated with no significant side effects.

Effects of Vitamin D Deficiency on Special Populations

Women of child-bearing age

Vitamin D deficiency has been associated with low birth weight babies.[40] Hollis described vitamin D deficiency in U.S. women of childbearing age as "a serious public health matter."[41] The Cochrane database of systematic reviews reports findings from two trials involving 232 women. In one trial the mothers had higher mean daily weight gain and lower number of low birth weight infants. In the other trial the supplemented group had lower birth weights. The authors concluded that there is not enough evidence to evaluate the effects of vitamin D supplementation during pregnancy.[42]

Breastfed infants

Infants are capable of producing all of the vitamin D they need in their skin during casual exposure to sunlight, provided the sunlight is of sufficient intensity.[43] Heavy skin pigmentation reduces the amount of vitamin D formed in the skin, which is why infants with dark skin pigmentation tend to be in less satisfactory vitamin D status than infants with light skin pigmentation and why they are at increased risk of vitamin D deficiency rickets.[43] A lack of supplemental vitamin D or inadequate sunlight exposure in breastfed

infants results in increased risk of developing vitamin D deficiency or rickets.[44] The recommended intake of vitamin D cannot be met with human milk as the sole source of vitamin D for the breastfeeding infant, because it contains about 25 IU/L or less of Vitamin D.[44] In light of growing concerns about sunlight and skin cancer and the various factors that negatively affect sunlight exposure, the American Academy of Pediatric recommends that all breastfed infants be given supplemental vitamin D.[44] Supplementation should begin within the first 2 months of life.[44] A daily intake of 400 IU of vitamin D is believed to prevent rickets reliably and is considered free of adverse effects.[43,45] The Institute of Medicine considers 200 IU per day to be an adequate intake for infants.[43] The following countries recommend higher levels of supplementation for infants: Bulgaria recommends 20 µg (800 IU) of vitamin D per day, Romania 10 µg (400 IU) and Canada 10 µg (400) [and 20 µg (800 IU) per day in the winter].[46] Canada has had this recommendation for over 10 years.[46]

Although prevention of rickets is the primary reason vitamin D supplements should be provided to breastfed infants, it is not the only reason.[43] Vitamin D receptors are present in many organs, and vitamin D exerts anti-proliferative effects, which may explain why it protects against colorectal cancer.[43] Also, vitamin D supplementation during infancy may protect against type I diabetes mellitus and has been shown to lead to higher bone mineral mass in prepubertal girls.[43]

African Americans

African Americans and other persons of color are at the highest risk of vitamin D deficiency. A study at Children's Hospital Boston revealed that 52% of African American and Hispanic adolescent boys and girls were vitamin D deficient.[47] Another study conducted by the Centers for Disease Control revealed that 42% of African American women ages 15 – 49 years were found to be vitamin D deficient throughout the United States at the end of the winter.[48] Holick, a pioneering researcher of vitamin D reported that 76% of African American women at the time they gave birth were vitamin D deficient and 81% of their infants were also deficient in vitamin D.[49] He also found in a sample of healthy men and women over the age of 65 in Boston that 34% of white, 42% Hispanic and 84% of African American men and women were vitamin D deficient.[6]

Skin pigmentation (melanin) in persons of color is a potent sun screen that provides protection from the damaging effects of sun light and decreases the amount of ultraviolet B radiation (UVB) that penetrates the skin.[50] The ultraviolet B radiation is what the skin uses to make vitamin D. Therefore, persons of color living in higher latitudes around the world are at particular risk, as are people living in Canada, Scandinavia, Russia, and all those whose lifestyles keep them from adequate access to sunlight when and where the sun is high in the sky.

According to Dr. Holick, a typical African American with a skin type 6 (refers to more melanin pigmentation and lowest risk of skin cancer)[6] has a 90% reduced capacity to produce vitamin D in their skin compared with the average "white" person.[50] In addition,

African Americans often have a lactase deficiency and avoid drinking milk which is one of the few foods that are fortified with vitamin D.[51] One reason that African Americans are at higher risk of developing breast and prostate cancer and having more aggressive forms of this disease compared to whites may be due to their higher incidence of vitamin D deficiency.[52,53] It has also been suggested that the increased risks of diabetes, hypertension and heart disease in African Americans may also be associated with the prevalence of vitamin D deficiency.[4,13]

The Elderly

Older adults (age > 50 years) are at greater risk of vitamin D deficiency than younger adults for several reasons. Physiologically, there are two concerns. The enzyme responsible for synthesis of 1,25(OH)2D in the kidney (the endocrine pathway) is resistant to parathyroid hormone (PTH).[2] This means that the 1-hydroxylase is not increased by PTH when there is need for calcium, so there is prolonged secondary hyperparathyroidism leading to increased bone loss. A low level of 25(OH)D exacerbates this hyperparathyroidism. Additionally, skin cells are less able to make cholecalciferol as there are fewer molecules of 7-dehydrocholesterol (provitamin D3) in the epidermis. Skin production of vitamin D following a standard exposure to UVB light decreases with age due to decreased levels of 7-dehydrocholesterol when young and old subjects are exposed to the same amount of UVB, elderly subjects produce only one-third the amount of cholecalciferol.[2]

Upwards of 80% of the elderly is vitamin D deficient. It causes muscle weakness and osteoporosis that leads to falls with devastating vertebral, hip, and other bone fractures. Clinical studies have demonstrated that vitamin D with and without calcium supplementation reduces fracture risk and falls in the institutionalized elderly and in individuals over the age of 65 living at home.[54]

Side Effects of HyperVitaminosis D

Intoxication of Vitamin D is very rare but can be caused by ingestion of excessively high doses, whether intentional or not.[24] Doses of more than 50,000 IU per day raise levels of 25-hydroxyvitamin D to more than 150 ng per milliliter (374 nmol per liter) and are associated with hypercalcemia and hyperphosphatemia.[24] Doses of 10,000 IU of vitamin D3 per day for up to 5 months, however, do not cause toxicity.[24]

The result of vitamin D intoxication is primarily elevation of the calcium levels in the blood, which could cause stone formation in the body tissues (over time), including urinary stones. With very high calcium levels one develops a type of diabetes, or frequent urination, in which calcium causes the same effect on the urinary system as does sugar in diabetes mellitus. The hypercalcemia is corrected by stopping vitamin D supplementation.[55]

Vitamin D Requirements

Current guidelines established by the National Academy of Sciences recommend daily values of 200 IU (International Units) for children and adults up to age 50, 400 IU for adults ages 51-70, and 600 IU for adults over 70. However, many experts believe that a daily dosage of 1000 IU or greater may be more beneficial.[7,26,56] A study by Glerup et al, examined the estimated amount of oral vitamin D intake necessary to maintain adequate sunlight exposure in sunlight deprived individual, and suggested that the daily oral intake of vitamin D should probably be 1000 IU per day.[57] Another expert, Professor Walter Willett, chair of the Harvard School of Public Health's nutrition department, says adults should be getting 800-1,000 IU of vitamin D per day.[58] The National Academy of Sciences has set 2,000 IU daily as the "tolerable upper limit" for vitamin D.[58]

Why are current efforts to address Vitamin D deficiency not sufficient?

In addition to sun exposure, the body gets vitamin D in two other ways – from foods and from pharmaceutical supplementation. The reality is that very few foods are rich in vitamin D except fatty fish such as salmon and mackerel, and fortified foods such as milk and some brands of orange juice.[14] Studies have also shown that it is difficult to obtain adequate levels of vitamin D in a balanced diet in order to protect the body against many diseases.[6] Vitamin D can be obtained through adequate intake of supplements.[59] Leading researchers tend to agree that this is a simple, safe, effective, and inexpensive way to maintain adequate levels of vitamin D in areas far from the equator. Studies show that the elderly may particularly benefit from vitamin D supplementation to maintain strong bones and to prevent falls.[60]

In 2005, Hollis advocated for establishing a new effective dietary intake recommendation for vitamin D.[61] Recently, a group of 12 prominent scientists signed a consensus statement calling for higher vitamin D status for individuals in North America. They report that this can be achieved by increased oral intake of vitamin D3 in the amount of 1000-2000 IU per day. Through GrassrootsHealth – a Public Health Promotion Organization of California, the scientists call for a higher level of support for research on the role of vitamin D for the prevention of cancer, in particular. Further information can be found on the organization's website – www.grassrootshealth.org.

Further, committees of experts were convened by the Institute of Medicine to set daily nutrition requirements and also to calculate the Tolerable Upper Intake Level for vitamin D at 2,000 IU per day.[62] Some of the same experts who think that Americans should have a lot more vitamin D in our diets are saying that upper limit needs to be increased because, at its current level, it may be scaring people off so they do not get the vitamin D they need.[62] An article published in the January 2007 *American Journal of Clinical Nutrition* reviewed dozens of vitamin D toxicity studies, including some that involved volunteers taking a mega dose of 100,000 IU a day.[62] The authors concluded that the upper limit for daily intake of vitamin D could safely be set at 10,000 IU.[62] Additionally, a group of 15 nutrition experts cited the study in an editorial in the March 2007 issue of the same journal that called for an overhaul of vitamin D guidelines, although they stopped short of recommending definite amounts.

The experts noted that 400 IU does not increase the amount of vitamin D circulating in the blood very much. Depending on how much a person started out with, they said a daily intake of about 2,000 IU -- the upper limit is necessary before blood levels get high enough for vitamin D to have its full disease-fighting effects.[62] It is known that 100 IU of vitamin D will increase serum 25(OH)D levels by 1 ng/ml.

Supplementation as an intervention

Besides adequate exposure to sunlight, and eating food rich in Vitamin D, dietary supplements provide another source of intake as noted above under Dietary Supplements. In 2006, Garland et al noted that the cost of 1000 IU of vitamin D3 is less than five cents, balanced against the huge human and economic costs of treating cancer attributable to vitamin D insufficiency.[26] Many other examples can be cited to underscore the benefits of adequate levels of vitamin D.[26,63]

Previous APHA Statements

Previously, APHA had a statement that briefly mentioned vitamin D in relation to infant feeding (1980, policy n. 8022) and ensuring urging mothers and caretakers of infants to provide vitamin D and fluoride as the only vitamin-mineral supplements. Yet, too few health care practitioners, public health professionals and the public-at-large have adequate information/knowledge about the benefits of vitamin D in protecting against many chronic diseases and its promise in decreasing health disparities.

Action Statements

Therefore the American Public Health Association:

1. Urges the Centers of Disease Control and Prevention to advocate and provide funding for a coordinated and integrated approach to **educating health care providers/practitioners** about the science and benefits of adequate levels of vitamin D.

2. Urges the United States Department of Agriculture (USDA) and other Federal agencies to promote the 2005 ***Dietary Guidelines for Americans*** as the scientific basis for **increased public awareness** using current nutrition guidance for healthy eating, notably for populations at greater risk for vitamin D deficiency/insufficiency.

3. Recommends to the Department of Human Health Services and USDA that the APHA have organizational representation on the panel of the *2010 Dietary Guidelines for Americans* in the next year, and beyond, for formulation of dietary guidelines to assist with **implementing vitamin D supplement recommendations nation-wide.**

4. Requests that it become a participating organization in planning Healthy People 2020 to **promote national awareness** of the magnitude of the problem of poor vitamin D status; and the associated increased risk for chronic disease

development by introducing specific objectives in planning Healthy People 2020 goals.

5. Urges Congress to appropriate funds to conduct **research** in diverse populations to determine population specific vitamin D intakes needed to produce and maintain optimal vitamin D status associated with reduced risk of chronic diseases.

6. Recommends to the Food and Drug Administration to add vitamin D to the list of required nutrients appearing on the **Nutrition Facts Panel** that is required on all foods in the U.S. market place.

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