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Extraskeletal Effects of Vitamin D: Potential Impact on WV Disease Morbidity and Mortality

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Abstract

Vitamin D is an essential nutrient and a secosteroid hormone that regulates many physiologic processes beyond calcium and bone homeostasis. These "extraskeletal" effects are impacted by the circulating levels of the storage form of vitamin D, 25-hydroxyvitamin D3. Levels of vitamin D can be detected after completing a simple 25(OH)D blood test. Vitamin D deficiency (<30 ng/mL) is associated with a higher risk of many chronic diseases including, but not limited to, fourteen types of cancers, type 1 and 2 diabetes mellitus, obesity, cardiovascular disease, hypertension, stroke, and asthma. This article explores the association between vitamin D deficiency and the burden of chronic diseases in West Virginia.

Introduction

Vitamin D has well-established roles in calcium and bone homeostasis. Recently, this necessary nutrient has been shown to regulate many other disease and metabolic processes. These "extraskeletal" effects of vitamin D include potential beneficial effects on the prevention of cancer, obesity, diabetes, cardiovascular disease, stroke, and asthma. These diseases burden West Virginia with significant impact on morbidity and mortality (**Table 1**).

Many variables affect these chronic diseases. West Virginia leads the nation in the following: current smokers (25.6%), limitation in physical activity (27.1%), insufficient sleep and rest (52.6%), and self reported poor health (25.8%).[1] West Virginia ranks second in the nation for obesity (32.5%) and for percent of population > 65 years of age.[1-4] In addition, West Virginia has one of the lowest yearly solar irradiance rates in the country which affects the cutaneous synthesis of vitamin D (**Figure 1**).[5]

The principal mechanism for synthesis of the storage form of vitamin D, a potent fat-soluble secosteroid hormone, is skin exposure to sunlight, a mechanism that is less efficient with increasing age.[6] Cutaneous production of vitamin D is dramatically altered by sunblock application (SPF 15; 99% reduction in synthesis) and seasonal effects due to location with negligible production from mid-October to mid-March in West Virginia (**Figure 2**).[6] Additionally, an increase in body mass index (BMI) decreases the bioavailability of fat-soluble vitamin D with a 1% increase in BMI associated with a 5% decrease in serum vitamin D levels.[6,7,8] As obesity increases in West Virginia, so does the risk of vitamin D deficiency. All of these factors (inactivity, obesity, location and age) make the risk of vitamin D deficiency greater for our population.

The storage form of vitamin D, 25-hydroxyvitamin D3 or 25(OH) D, can be determined with a simple blood test with deficiency defined

Table 1. ***Important WV chronic diseases affected by Vitamin D levels.[1]***

Disease (alphabetical)	Prevalence in WV	Vitamin D connection
Asthma	8.8%	Yes
Cancer	10.4%	Yes
Diabetes	12.4% (1st highest in US)	Yes
Heart Disease	10.3% (1st highest in US)	Yes
Hypertension	38.4% (2nd highest in US)	Yes
Obesity	32.5% (2nd highest in US)	Yes
Stroke	3.7% (3rd highest in US)	Yes

Objectives

The objective of this article is to explore the association of vitamin D deficiency on major contributors to West Virginia disease morbidity and mortality.

as less than 30 ng/mL.[11] Vitamin D deficiency reportedly affects about 50% US adults, with up to 54% deficiency prevalence noted among adolescent females.[12-15] Because of increasing evidence linking vitamin D deficiency with chronic diseases, diagnosis and prevention beginning in childhood is paramount.

The purpose of this review article is to use current data to explore the association between vitamin D deficiency and the burden of chronic diseases in West Virginia.

Normalcy

The human body uses about 3000 to 5000 IU vitamin D3 per day.[16] If cutaneous synthesis is altered (sunblock, season, age, skin coloration and disease states), it is very difficult to obtain this amount from a non-supplemented diet, even with a diet rich in fatty wild-caught fish.[6,14,17] Because of this, numerous health care leaders have proposed a dramatic increase in the adequate intake of vitamin D over current recommendations.[18] Many of the supplementation protocols used in studies cited in this manuscript have not accounted for the discrepancy in total daily use (4000-5000 IU/d) and recommended adequate intake (from 200 IU/d to 600IU/d; dependent on age and pregnancy) of vitamin D3. We therefore have placed more emphasis on studies that have conclusions based on direct testing of 25(OH)D and its impact on chronic diseases.

Cancer

The prevalence of cancer in West Virginians is 10.4%.[1] Numerous studies have shown a correlation between 14 cancers, including colorectal, breast, and prostate, and vitamin D deficiency.[19] Data is inconsistent regarding vitamin D supplementation and lowered cancer risk. For example, the

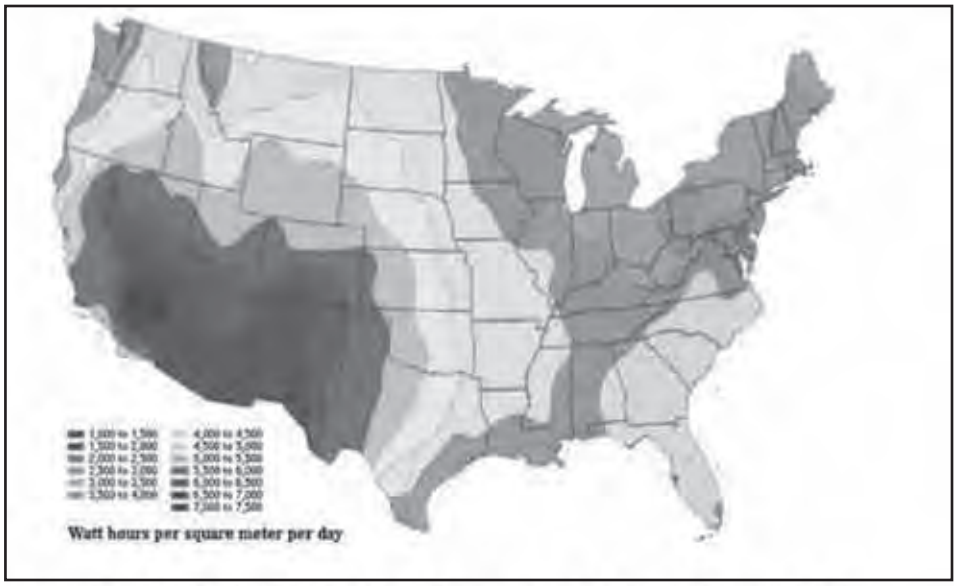

Figure 1.
United States Solar Irradiance Map. The average yearly solar irradiance in Watt/hr is demonstrated. West Virginia has one of the lowest rates in the contiguous US. Source: National Renewable Energy Laboratory.[3] Available at http://www.nrel.gov/gis/solar.html

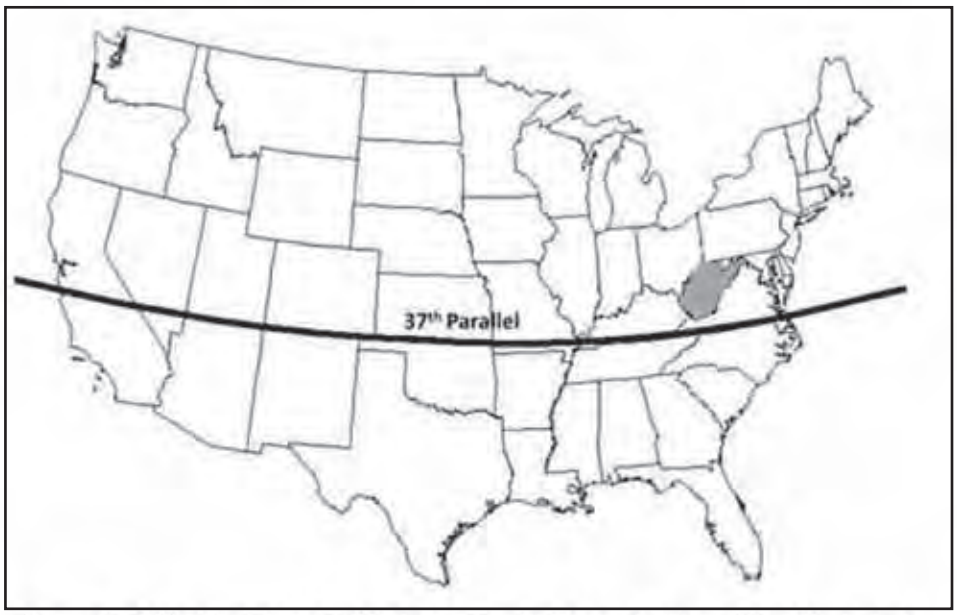

Figure 2.
37th Parallel and effect on vitamin D production. *West Virginia is above the 37th parallel resulting in negligible cutaneous production of vitamin D from mid-October to mid-March. When the leaves are falling, so are 25(OH)D levels. There is a direct correlation with vitamin D deficiency and distance from the equator.[9,10]*

Women's Health Initiative showed supplementing 400 IU of vitamin D3 combined with 1000 mg calcium daily to have no effect on the incidence of colorectal cancer or breast cancer.[20,21] Lappe et al. showed a significant reduction in all-cancer risk for women taking 1100 IU of vitamin D3 and 1500 mg of calcium supplementation.[22] The direction of association is dependent on sufficient levels of 25(OH)D.

Cancer risk is decreased when levels of 25(OH)D are at least 32 ng/mL.[23] Gorham et al., demonstrated a 50% reduction in colorectal cancer risk at 33 ng/mL 25(OH)D with a World Health Organization (WHO) working group identifying colon cancer as the greatest risk associated with poor vitamin D status.[24] Garland et al., showed a 50% reduction in breast cancer risk at 52 ng/mL 25(OH)D.[25] In general, the levels of circulating 25(OH)D needed to reduce cancer risk in the population are much higher than current vitamin D adequate intake recommendations.

Cardiovascular disease (CVD), Hypertension, Stroke

West Virginia has the highest rate of cardiovascular disease in the US; 10.3% of our population has symptomatic coronary artery disease.[1] The mechanisms in which vitamin D may lower cardiovascular risk have not been fully elucidated, but many possible mechanisms have been proposed. For hypertension, the renin-angiotensin-aldosterone system (RAAS) appears to be suppressed by vitamin D with the risk of hypertension increasing from south to north in the Northern hemisphere.[26,27] Thus, a deficiency may lead to hypertension, a risk factor for CVD. Deficiency of vitamin D is associated with poor glycemic control[28], another risk factor for CVD. The presence of vitamin D decreases inflammatory markers and even increases anti-inflammatory markers, each of which is beneficial to the cardiovascular system.[29,30] Vascular smooth muscle and endothelium responds to vitamin D in a cardioprotective way by decreasing smooth muscle cell proliferation[31], inflammation[16], and thrombosis.[33] Each of these is a risk factor for cardiovascular disease. Unfortunately, adequate clinical trials looking at vitamin D supplementation with cardiovascular endpoints are lacking. The Framingham Offspring Study demonstrated an 80% greater risk for cardiovascular disease when vitamin D levels were less than 10 ng/mL compared to participants with a 25(OH)D level greater than 15 ng/mL.[34] Both the Nurse's Health Study and the Health Professionals Follow-up Study found an increased incidence of hypertension when 25(OH)D levels were below 15 ng/mL compared to levels above 30 ng/mL.[35]

A more recent study showed post-menopausal women with 25(OH)D3 levels <20 ng/mL to have increased cardiovascular risk factors as well as an increased risk of cardiovascular disease, cerebrovascular disease, and death when compared to the non-deficient (>20 ng/mL 25(OH) D3) group. Another recent study, which followed suspected acute coronary syndrome patients for 2 years, reported an inverse relationship with death within that 2 year period and vitamin D status. Clearly, vitamin D plays a role in the health of the vascular system, but research to determine the optimal level of vitamin D and the role of supplementation is needed.[36]

Clinical trials examining the effect of Vitamin D supplementation on blood pressure have variable results. One meta-analysis of 8 clinical trials demonstrated a significant 3.1 mmHg reduction in the diastolic pressure with a non-significant 3.6 mmHg reduction in systolic pressure when vitamin D was supplemented.[37] Another meta-analysis of 10 trials found that most did not show statistically significant effects on blood pressure.[38] Meta-analysis of trials investigating the effects of vitamin D supplementation on cardiovascular outcomes, including myocardial infarction, stroke, and other cardiac and cerebral outcomes showed no statistically significant effects.[38] Trials performed to date, however, have significant variation in the vitamin D levels that were used to define insufficiency, measured outcomes, doses used, and identified confounders.[38]

Multiple studies have demonstrated an association between vitamin D insufficiency and cerebrovascular disease mortality with one recent study showing twice the risk of stroke from lowest (<9.8 ng/mL 25(OH) D) to highest quartile (>21.5 ng/mL 25(OH)D).[39,40,41] Carrelli et al. found a correlation between carotid atherosclerosis, a major risk factor for stroke, and 25(OH)D status.[42] A population-based study found data that suggests a reduced intake of vitamin D in elderly patients, along with low serum concentrations of 1,25-dihydroxyvitamin D, leads to an increased risk for future strokes.[43] With numerous studies revealing an association between vitamin D status and cerebrovascular risk, future research should be directed at determining whether a causal relationship exists through clinical supplementation trials.

Asthma

Asthma is a chronic inflammatory airway disease caused by a combination of environmental and genetic factors. In recent years, the prevalence of children with asthma was significantly higher in WV than the nation as a whole. According to a CDC report based on 2009 data, around 9% of West Virginians carried a diagnosis of asthma.[1] With such a strong prevalence, it is crucial to continually seek new methods to treat and reduce the incidence of this common disease.

Vitamin D receptors are located in multiple lung cell types and have beneficial effects on asthma control. Several mechanisms are used to promote these effects including reducing hyperplasia and airway

smooth muscle proliferation, decreasing inflammation, promoting lung immunity, slowing cell cycling, and enhancing the effects of exogenous steroids.[44,45] An inverse relationship between vitamin D status and serum IgE levels was demonstrated by Ma and Zhen.[46] This supports the idea that vitamin D deficiency is related to increased risk of asthma and allergy.[47] A study by Alyasin et al. in 2011 showed that serum 25(OH)D levels were inversely associated with asthma.[48] This was a cross-sectional study conducted with children and, after adjusting for age, BMI, and sex, the correlation between vitamin D and asthma increased. The study also found a significant relationship between pulmonary function test outcomes, such as FEV1 and FEV1/FRC, and vitamin D levels. Similarly, a case control study by Ehlayel et al. in 2011 suggested a link between vitamin D deficiency and development of asthma and allergic diseases.[49] Vitamin D levels were lower in asthmatic children than in control subjects.[49] Furthermore, a Chinese case-control cohort study revealed that genetic polymorphisms of vitamin D binding protein increase the susceptibility of asthma within the Chinese Han population.[50] Searing et al. demonstrated *in vitro* that vitamin D can enhance the action of glucocorticoids on inflammation.[51] Thus, correction of vitamin D deficiency, which is often associated with asthma, could be a possible therapeutic option for glucocorticoid resistant asthma. The exact role 25(OH)D plays on the pathogenesis of asthma is still under investigation, but a significant correlation has been made to higher serum levels of vitamin D and reduction of asthma.

Diabetes and Metabolic Syndrome

West Virginia ranks among the highest in the nation for prevalence of diabetes with estimates for adults approximately 12.4%.[1] West Virginia also ranks second nationally for obesity rates with a prevalence of 32.5%.[1] Several studies show an inverse relationship between BMI and concentrations of 25(OH)D.[7,8] Because vitamin D is fat soluble, it is readily taken up by fat cells, and this sequestration of vitamin D likely plays a large role in its decreased bioavailability.[8] Decreased levels of 25(OH)D associated with higher BMI may play a key role in insulin resistance and thus type-2 diabetes in metabolic syndrome. Research in this area is relatively new, and there are some conflicting findings. One analysis showed an association between higher vitamin D concentrations and a reduced risk for developing type 2 diabetes mellitus in men only.[52] Chiu et al. found increased risk for metabolic syndrome with lower 25(OH)D levels.[28] Additionally, they found that vitamin D is

directly associated with insulin sensitivity and release from beta-cells.[28] Unfortunately, randomized trials investigating the effects of vitamin D supplementation have failed to consistently demonstrate a beneficial effect on insulin resistance or insulin secretion.[53] Most of these studies were very short in duration (4 days to 2 years), which may not be long enough to show clinically significant beneficial effects.

Vitamin D receptors are present in activated T and B-lymphocytes and in activated macrophages, which make up a portion of our immune response. Mouse models were used to show that reduction in the incidence of type 1 diabetes was achieved if the mice received 1,25$(OH)_2$D3 early in life.[54] Of note, the autocrine production of the locally active form of vitamin D, 1,25$(OH)_2$D3, is critically dependent on adequate concentration of 25(OH)D.[55] Another study in by Hyppönen et al. followed a cohort of children for the first 31 years of life. They observed that children who received 2000 IU vitamin D during their first year of life decreased their risk of developing type 1 diabetes by 78% compared to children who did not receive supplementation.[56] A meta-analysis by Zipitis and Akobeng demonstrated significant reduction in the incidence of type 1 diabetes with supplementation of vitamin D in the first year of life.[57] Follow-up studies are needed to establish the best treatment regimen for vitamin D supplementation.

Vitamin D Levels for Extraskeletal Benefit

Currently, vitamin D intake recommendations are based solely on bone health and do not consider the potential extraskeletal benefits of higher vitamin D levels. Bischoff-Ferrari et al. suggested target concentrations of at least 30 ng/mL, with ideal levels of 25(OH)D around 36-40 ng/mL.[58] They also estimated that to bring half the population to the ideal concentration of 25(OH)D, daily intake between 700 and 1000 IU of vitamin D would be required.[58] Lappe, however, estimated optimal levels of 25(OH)D to be as low as 30-32 ng/mL.[55] Heaney projected that supplementing the entire population with 2000 IU/day of vitamin D3 would result in at least 80% of the population having a 25(OH)D level greater than 32 ng/mL.[59] Daily intake and production of vitamin D varies widely with age, BMI, outdoor activity level, sunblock use, various disease states (e.g. kidney or liver disease preventing key hydroxylation reactions), time of the year, and latitude.[6] The only way to diagnose and safely treat vitamin D deficiency is to measure serum 25(OH)D. Unfortunately, insurance coverage for measurement is limited.[55] Current indications for obtaining 25(OH)D levels are listed in Table 2. Laboratory testing reimbursement can occur up to 4 times per annum with levels determined following supplementation protocols to correct vitamin D deficiency.

There are three ways to impact vitamin D stores: sun exposure, diet or supplementation. In people with light skin coloration, sun exposure below the minimal erythemal dose (skin redness) is usually enough to make sufficient daily vitamin D requirements. This is typically about 10 minutes during the day from 10:00 am to 3:00 pm without sunscreen and with minimal clothing (i.e. swimsuit).[55] However, at latitudes above 37 degrees North, from mid-October to mid-March, no vitamin D is made cutaneously due to the steep solar angle.[55] (**Figure 2**) Current public sensitivity connected to sun exposure is worth noting. Early studies demonstrated that skin cancer rates increased with sun exposure, however, non-skin cancer rates actually decreased.[60,61,62] Additionally, one should emphasize that many of our vital processes have an evolutionary dependence on sun exposure and vitamin D production (e.g. immunity) with over 20 photoactive products produced cutaneously following sun exposure.[6,63] The ultimate effect of blocking normal cutaneous photoproduct synthesis with sunblock is not known.

Table 2. ***Indications for 25(OH)D Testing that may be eligible for Medicare Reimbursement.***[55]

Disorders of parathyroid gland	Other hyperparathyroidism
Hypoparathyroidism	Rickets, active
Osteomalacia, unspecified	Unspecified vitamin D deficiency
Disorders of phosphorus metabolism	Disorders of calcium metabolism
Chronic kidney disease (CKD)	Secondary hyperparathyroidism (of renal origin)
Osteoporosis	Other osteoporosis
Disorder of bone and cartilage, unspecified	Paget's Disease
History or risk of falls	Fibromyalgia
Malabsorption syndrome	History of bariatric surgery
Liver Disease	Anticonvulsant use

The second way to alter vitamin D status is through diet. Many foods are fortified with vitamin D, and foods such as wild-caught salmon, tuna, cod liver oil, and beef liver naturally contain vitamin D. However, NHANES III data demonstrate that diet supplies very little of the 4000 to 5000 IU of vitamin D3 used per day.[15]

The third way to affect vitamin D status is supplementation. One should know that both D2 (plant) and D3 (animal) are available over the counter with D3 more effective in raising 25(OH)D levels.[64,65] We recommend following current recommendations for supplementation and testing protocols as highlighted in the *New England Journal of Medicine*.[6]

Conclusion

Vitamin D receptors are located in many cell types throughout the body, and vitamin D plays a regulatory role in many physiologic processes. Low levels of the storage form of vitamin D, 25(OH)D, are correlated with higher risk of many diseases including, but not limited to, asthma, cancer, type 1 and 2 diabetes mellitus, obesity and metabolic syndrome, cardiovascular disease, hypertension, and cerebrovascular disease. These diseases in particular have a high prevalence in West Virginia as well as the U.S. With the current epidemic of hypovitaminosis D, it is essential to test for and correct this modifiable risk factor by educating patients about appropriate sun exposure, proper nutrition, availability, and proper usage of vitamin D supplements.

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