

Protean Manifestations of Vitamin D Deficiency, Part 1: The Epidemic of Deficiency

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Abstract: Just when vitamin deficiencies were thought to be a “thing of the past” a new vitamin deficiency—that of vitamin D has developed over the past 20 years. Vitamin D works like a hormone being produced primarily in one organ (the kidney) before circulating through the bloodstream to multiple organs where it has multiple effects. The increased prevalence of vitamin D deficiency is due to changes in modern lifestyle—mainly lack of exposure to sunlight and the increased prevalence of obesity that, results in sequestration of this fat-soluble vitamin in adipose tissue. Distance from the Equator and increasing age and skin pigmentation are additional risk factors. In pregnancy vitamin D deficiency can result in low birth weight, pre-term labor, pre-term birth, infections, and pre-eclamptic toxemia. While vitamin D deficiency is classically associated with rickets and osteomalacia, its effects are much more protean.

Key Words: Autoimmune disease, cancer, cardiovascular disease, diabetes, vitamin D

Key Points

- Vitamin D deficiency is mainly due to obesity and lack of sun exposure.
- Vitamin D deficiency is associated with autoimmune diseases (multiple sclerosis, type 1 diabetes, type 2 diabetes, metabolic syndrome, cardiovascular disease, cancer).
- Causation has not been proven in this condition but evidence of causation is accumulating.

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In recent years it has become obvious that the addition of a vitamin supplement, when the vitamin is not deficient, is not advantageous and may even be harmful. Until recently in modern Western society it was believed that vitamin deficiencies were a “thing of the past,” but in the past 20 years, changes in lifestyle have led to a new vitamin deficiency—that of vitamin D. In addition, evidence that the effects of vitamin D deficiency are not confined to bone but are protean, affecting multiple organs and systems, has been accumulating. In contrast, evidence that correction of vitamin D levels into the normal range will prevent, ameliorate, or cure the diseases associated with vitamin D deficiency is sparse but is slowly but surely accumulating.

Physiology of Vitamin D

Vitamin D works like a hormone because it is produced primarily in one organ (the kidney) before circulating through the bloodstream to organs where it has wide-ranging effects.¹ External sources of vitamin D are foods such as cheese, butter, margarine, fortified milk, fish, fortified cereals, and vitamin supplements.² However, the majority of vitamin D comes not from the diet but from manufacture in the dermis when the skin is exposed to solar ultraviolet (UVB) (290–315 nm) light. Through this exposure, which has photochemical and thermal effects, cholecalciferol (vitamin D₃) is manufactured from 7-dehydrocholesterol. Unlike excess oral intake overexposure to sunlight cannot cause vitamin D toxicity because UVB also converts any excess vitamin D₃ to inert isomers.

Vitamin D₃ is hydroxylated in the liver to 25-hydroxy-vitamin D₃, and in the kidney and other tissues. 25-OH-vitamin D₃ is further catalyzed by the enzyme 1 α hydroxylase to its active form 1-25-OH-vitamin D₃. 1-25-OH-vitamin D₃ penetrates the cell membrane entering the cytoplasm of the cell from which it crosses into the nucleus to attach to its receptor.³ Receptors for 1-25-OH-D₃ are situated in the nuclei of cells of multiple organs and activation of these receptors results in an increased expression of more than 200 genes, all of which increase the expression of CYP27B1. This can also be increased by immune inputs, such as those from Toll-like receptor signaling. The result of CYP27B1 expression, whether due to 1-25-OH vitamin D or an immune input, is the production of

the intracellular proteins, which are ultimately responsible for the protean actions of 1-25-OH vitamin D.⁴

The classic effect of vitamin D activity is in the gastro-intestinal tract where 1-25-OH vitamin D is a key component of calcium homeostasis through regulating calcium absorption. When serum calcium drops, the calcium receptor on the parathyroid gland is activated, which increases the production and release of parathyroid hormone (PTH). PTH has both an instantaneous and extended effect. The instantaneous effect occurs through activation of the PTH receptor in bone, which rapidly mobilizes calcium so that hypocalcemia and its manifestations are avoided. The extended effect of PTH is to replenish the calcium pool by increasing the conversion of 25 to 1-25-OH vitamin D in the kidney, which through activation of the 1-25-OH vitamin D receptor in the intestine increases calcium absorption.¹

Defining Vitamin D Deficiency

Because of the long half-life of 25-OH vitamin D, its level is used to assess vitamin D deficiency. The active form of vitamin D, 1-25-OH vitamin D, will if renal function is normal, almost always be in the normal range even when severe vitamin D deficiency is present.² Normal 25-OH vitamin D levels are enjoyed by those who work outdoors; levels between 42 and 65 ng/mL have been documented.⁵ Humans originated in equatorial East Africa, where in an unclothed state they received year-round sun exposure. An East African tribe, the Masai, have 25-OH-vitamin D levels in the 50–80 ng/mL range, which may be assumed to be a normal range. However, if a normal level is based on two standard deviations in a modern Western society, then an abnormal 25-OH-vitamin D level is below 10 ng/mL.

Based on its biological effects, a normal 25-OH vitamin D level is ≥30 ng/dL. Insufficiency is defined as a 25-OH vitamin D level of 20–29 ng/dL, deficiency as a 25-OH vitamin D level of 10–19 ng/dL, and severe deficiency as a 25-OH vitamin D level of <10 ng/dL (Table 1).⁶ Based on PTH levels the World Health Organization (WHO) defines vitamin D deficiency as a serum 25-OH vitamin D of <20 ng/dL and insufficiency as a 25-OH vitamin D level of <30 ng/dL.⁷ Unfortunately, many studies have shown large variations in PTH levels when 25-OH vitamin D levels are clearly in the

deficient range as well as when intestinal calcium absorption is decreased.^{8,9}

Causes of Vitamin D Deficiency

While vitamin D deficiency may occur due to decreased vitamin D intake or to malabsorption such as that which occurs with hepatic, pancreatic, and celiac diseases, the major cause of vitamin D deficiency is inadequate sun exposure. Decreased sun exposure is caused by avoiding sunlight, by covering the skin with clothes, or by utilizing sunscreens.¹⁰ Exposure to sunlight is also governed by one’s occupation or geographic location. In winter months humans, no matter how fair skinned, cannot manufacture vitamin D at latitudes above 35°N; and at any time of year the ability to manufacture vitamin D is inversely proportional to both the degree of skin pigmentation and age.^{11,12} For example, African Americans tend to have lower 25-OH vitamin D levels than Americans of European origin.¹³ Historically only fair-skinned people could survive at higher latitudes because of their ability to manufacture sufficient vitamin D3. The exception to this rule is the dark-skinned Inuit people, who survived because of a high dietary intake of vitamin D from fish and animal livers. With aging the ability of skin to manufacture vitamin D declines, so that by age 65 the capacity to produce vitamin D3 is reduced by 75%.¹²

In modern times, especially in the Western world, the most common cause of vitamin D deficiency is obesity. This is because vitamin D is a fat-soluble vitamin that in obese people, even with adequate sunlight exposure and dietary intake, becomes sequestered in adipose tissue, where it is ineffective.^{14,15}

Who Has Vitamin D Deficiency?

Worldwide, vitamin D deficiency is estimated to be present in more than 1 billion people. Somewhere between 40 and 100% of US and European elderly adults have also been shown to be vitamin D deficient. Even in Hawaii, where the average sun exposure is 11 hours per week, 50% of adults are deficient in vitamin D, probably due to skin pigmentation and obesity. In the National Health and Nutrition Survey between 25% and 57% of Americans were vitamin D deficient, and in a hospital survey 57% of patients and 20 to 51% of internal medicine residents were vitamin D deficient.^{16–18} Vitamin D deficiency is also present in 24% of adolescents and 32% of young adults. A total of 9% of US children are vitamin D deficient and 61% have vitamin D insufficiency.^{19,20} Risk factors for vitamin D deficiency in US children include being African American or Latino, being older, having a poor intake of milk, and spending more than four hours per week watching television or playing video games.¹⁹ Vitamin D deficiency has also been shown to be present in 47.8% of lactating and 50% of postmenopausal women.^{21,22}

The major reasons for the increased prevalence of vitamin D deficiency, when compared with earlier studies in the United States, are decreased milk consumption, decreased

Table 1. Levels of vitamin D deficiency	
Status	25-OH-Vitamin D level, ng/dL
Normal	>30
Insufficiency	20–29
Deficiency	10–19
Severe deficiency	<10

exposure to sunlight, increased numbers of non-European races, and particularly, the increase in the prevalence of obesity.²³ Vitamin D deficiency is also more prevalent when chronic diseases are present; for example, 87% of people with HIV and 86% of those with chronic kidney disease have vitamin D deficiency.²⁴

Vitamin D Deficiency and Pregnancy

Worldwide prevalences of vitamin D deficiency during pregnancy range from 18% to 84%, depending upon the distance from the Equator and the percentage of skin covered by clothing.²⁵ In the United States the prevalence is lower (between 5% and 50%) but is much higher in African American women (54.1% versus 29.2%) and these prevalences persist even when prenatal vitamins have been utilized.²⁶ As would be expected with the high prevalence of vitamin D deficiency in African American mothers, their offspring at delivery have a higher prevalence of vitamin D deficiency (45.6% versus 9.7%). Gestational vitamin D deficiency has also been associated with low birth weight and reduced fetal bone mineral content^{27,28} and an increased risk of preterm labor, preterm birth, infections, and severe eclampsia.^{29–31} Gestational vitamin D deficiency has also been associated with increased wheezing in the offspring during the first years of life.³¹ Furthermore, the presence of autoantibodies to the insulin-producing beta cell of the pancreas in newborns is inversely associated with maternal vitamin D intake, which may be why childhood vitamin D supplementation has been shown to decrease the incidence of type 1 diabetes.

In most infants vitamin D stores acquired in utero are depleted by eight weeks. Babies who are breast-fed, compared with those who are formula-fed, are at increased risk of vitamin D deficiency because human breast milk contains minimal vitamin D, and 47% of untreated lactating women become vitamin D deficient.^{22,32} Because of the high risk of vitamin D deficiency in breast-fed infants the American Academy of Pediatrics has recommended that exclusively breast-fed infants be supplemented with 200 IU of vitamin D daily beginning after birth and maintained through childhood and adolescence.³³

Rickets, Osteomalacia and Beyond

In the 17th century both Whistler and Glisson described rickets, which was characterized by growth retardation, bending of the spine, deformities of the legs, and weak, toneless muscles, using autopsy studies that showed impaired mineralization of the epiphyseal growth plate cartilage.³⁴ In 1919, the cause of rickets was identified by Sir Edward Mellanby as being due to vitamin D deficiency.³⁵ Subsequently, decreased mineralization of newly formed bone (osteomalacia) in adults was also shown to be due to vitamin D deficiency and was classified as being a mild form of rickets.

Like bone, multiple organs have nuclear 1-25-OH vitamin D receptors, these organs can be adversely affected by vitamin D deficiency. A classic example is fractures in elderly adults. The amount of osteoporosis is increased, which corresponds to an increase in vitamin D deficiency-induced neuromuscular dysfunction and thus an increase in falls and fractures. A meta-analysis of six studies of vitamin D supplementation in the elderly showed that a daily intake of 800 IU of vitamin D per day resulted in a significant reduction in the frequency of falls.³⁶

Beyond Rickets and Osteomalacia

Other important activities of 1-25-OH vitamin D through its nuclear receptors are regulation of cell growth and modulation of the immune system. 1-25-OH-vitamin D regulates the growth of both normal and neoplastic cells, and this is the probable reason for the increased incidence of cancer in vitamin D-deficient subjects.³⁷ By modulating the immune system, 1-25-OH vitamin D regulates the activities of both the B and T lymphocytes, macrophages, and the thymus gland, which would explain why vitamin D deficiency is associated with autoimmune diseases, infections, and allergic reactions.³⁸ The inflammatory effects of vitamin D deficiency also play a major role in the association of vitamin D deficiency with type 2 diabetes and cardiovascular disease.

In conclusion, an epidemic of vitamin D deficiency has developed in the last 20 years due mainly to a lack of exposure to the sun and the increase in obesity. Vitamin D deficiency in pregnancy can have devastating effects. Although historically, vitamin D deficiency is associated only with rickets and osteomalacia, its effects are much more protean.

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Protean Manifestations of Vitamin D Deficiency, Part 2: Deficiency and Its Association with Autoimmune Disease, Cancer, Infection, Asthma, Dermopathies, Insulin Resistance, and Type 2 Diabetes

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Abstract: Vitamin D deficiency is epidemic and its manifestations are protean. Vitamin D deficiency is associated with autoimmune diseases (particularly multiple sclerosis and type 1 diabetes) and has been associated with infection, allergy, asthma, and dermatopathies (particularly psoriasis). Asthma may be worsened by vitamin D deficiency and correction of the deficiency has been shown to improve the manifestations of asthma. Vitamin D deficiency has been associated with multiple cancers, including those of the breast, colon, ovary, and prostate. Due mainly to increased insulin resistance but also to an impairment in insulin release, vitamin D deficiency is associated with the development of type 2 diabetes. In addition, the complications of diabetes may be worsened by vitamin D deficiency.

Currently largely due to decreased exposure to sunlight and the epidemic of obesity over the past twenty years there has been an epidemic of vitamin D deficiency. While vitamin D deficiency is classically associated with rickets and osteomalacia its effects are protean. In this article, I review some of these associations—autoimmune diseases, cancer, dermatopathies, infection, asthma, insulin resistance and type 2 diabetes.

Vitamin D Deficiency and Autoimmune Disease

When 1-25-OH vitamin D attaches to and activates its nuclear receptor there is a decrease in the formation of macrophages from monocytes and a reduced presentation of antigen containing macrophages to T lymphocytes. Synthesis of immunoglobulins by B lymphocytes and maturation of antigen presenting dendritic cells are also suppressed and delayed sensitivity reactions are inhibited by 1-25 OH vitamin D. Vitamin D receptor activation also has an anti-proliferative

effect on activated lymphocytes and suppresses the generation and activity of natural killer lymphocytes.^{1,2} The development of vitamin D deficiency results in reactivation of these inflammatory processes and an increased risk for auto-immune diseases. The suppression by 1-25-OH vitamin D of T cell activation and function is achieved through suppression of the T helper 1 (Th-1)-mediated inflammatory immune response which is a key component of vitamin D's capacity to block the development of Th-1 driven autoimmune diseases.³

Autoimmune diseases that have been associated with vitamin D deficiency include multiple sclerosis (MS), rheumatoid arthritis, Crohn disease, psoriasis and type 1 diabetes. In addition, polymorphisms of the genes for the vitamin D receptor have been associated with Hashimoto disease, Graves disease, and Addison diseases, but these autoimmune diseases have not to date been reported to be associated with vitamin D deficiency.^{4,5}

With type 1 diabetes the development of autoimmunity to pancreatic beta cells may even occur in utero when maternal vitamin D deficiency exists.⁶ In addition, vitamin D deficiency, which occurs especially in breast-fed infants, has been shown to increase the incidence of type 1 diabetes.^{7,8} In a Finnish study of 10,266 children who received 2000 IU of vitamin D daily for the first year of life, after 30 years the relative risk of developing type 1 diabetes was reduced by 78%.⁷

The availability of sunlight and the association of latitude with autoimmune diseases is best illustrated by the epidemiological patterns associated with MS. In a retrospective Australian study it was found that of all the cases of MS that were diagnosed between 1920 and 1950, there was a 30% higher risk of being diagnosed as having MS if the birth occurred in November and December than if the birth occurred in May and June.⁹ This corresponded to lower maternal sunlight exposure five to nine months before birth, and the results of this study initiated an Australian recommendation that supplemental vitamin D be given during pregnancy to avoid maternal vitamin D deficiency and MS in the offspring.¹⁰ Of

more than 35,000 pairs of mothers and daughters in the Nurses Mothers Study, 199 nurses developed MS. Comparing mothers who had the highest and lowest vitamin D intake during pregnancy, there was a significant 45% reduction in the development of MS in the daughters of mothers who during pregnancy had a high vitamin D intake. This study also showed that mothers who had a daily intake of four or more glasses of milk, when compared with those with an intake of less than three daily glasses, had a 45% lower risk of having a daughter develop MS.¹¹ The association of vitamin D deficiency with both obesity and autoimmune disease was shown in a prospective study in which women judged to be obese at age 18 had a 225% increased risk of developing MS.¹² Of veterans who develop MS, the onset is at an earlier age in residents of more northern latitudes and veterans with a history of a lower vitamin D intake.¹³

Vitamin D Deficiency and Infection

In the mid-19th century the power of sunshine to prevent and slow the progression of tuberculosis was recognized. Stimulation of the nuclear 1-25-OH vitamin D receptor results in the expression of anti-microbial peptides which reduce the growth of mycobacterium tuberculosis within the macrophages.¹⁴ Patients with active tuberculosis have been shown to have lower vitamin D levels in spite of the ability of the tuberculosis granuloma to increase the conversion of 25 to 1-25-OH vitamin D because of increased CYP27B1 expression and Toll-like receptor signaling.¹⁵ In active tuberculosis and sarcoidosis, the increased the conversion of 25 to 1-25 OH vitamin D may occasionally cause hypercalcemia.

The incidence of upper respiratory tract infection, regardless of the time of year, is progressively increased with vitamin D deficiency, with the increase being inversely proportional to 25-OH vitamin D levels.¹⁶ The most likely reason for the inverse relationship of vitamin D with infection is that vitamin D improves the efficacy of the barriers to infection that are present in the gut, lung, placenta, and skin. The improved efficacy of these barriers occurs because vitamin D increases the production of cathelicidin, a bactericidal protein. Decreased 1-25-OH vitamin D levels in monocytes and macrophages diminish the expression of genes that activate the Toll-like receptor pathway and the production of cathelicidin and other bactericidal proteins.¹⁷ Indeed it has recently been reported that patients (mostly elderly) who were hospitalized with clostridium difficile enteritis and had a 25-OH vitamin D level of <21 ng/dL, had a 36% 30-day clearance rate of clostridium difficile compared with 53% in those whose 25-OH-vitamin D level was above this level. In addition, the mortality rate was significantly higher (56% versus 33%) in those with lower 25-OH vitamin D levels.¹⁸

Vitamin D, Psoriasis and Asthma

Vitamin D deficiency, through its effect on the immune system, can result in the development of both atopic dermatitis

and psoriasis. The onset and the worsening of the features of dermatological psoriasis is associated with the winter months, northern latitudes, and vitamin D deficiency.¹⁹ A recent randomized controlled study of Irish patients with psoriasis who were given UVB light therapy three times per week during the winter months showed an improvement in the dermal manifestations of psoriasis, which was associated with an increase in vitamin D levels.²⁰ The study also showed that during winter months 75% of psoriatic subjects were vitamin D deficient.²⁰

A major allergic manifestation of vitamin D deficiency is asthma. Children taking inhaled glucocorticoids for asthma have been shown to have not only lower vitamin D levels but also higher IGE levels and inferior lung function.²¹ Vitamin D deficiency has an effect on increasing the Th1-Thi2 ratio balance, which causes smooth muscle contraction, airway inflammation, prostaglandin dysregulation, and airway remodeling. In vitro anti-inflammatory markers such as MKP-1 and IL-10 are decreased with the addition of vitamin D. In vivo, the response to dexamethasone in vitamin D-deficient asthmatics was improved tenfold when vitamin D levels were normalized, and in the repletion resulted in decreased utilization of inhaled and oral glucocorticoids as well as inhaled beta agonists. Indeed, for each 1-ng/mL increase in the serum 25-OH-vitamin D level, FEV₁ increased by 21 mL/minute, and when 25-OH vitamin D levels were corrected to above 30 ng/mL airway reactivity decreased by 50%.²² Furthermore, the dose of metacholine that was required to decrease the FEV₁ by 20% was decreased by 53.7% and MAP-kinase expression on mononuclear cells increased.²³ The prevalence of asthma has been shown to increase with an increasing body mass index which may be due to vitamin D deficiency.

Vitamin D and Cancer

The greater the distance from the Equator, the greater is the incidence and prevalence of cancer. Furthermore, cancer survival has been shown to be improved in both hemispheres if the cancer was diagnosed during the summer months.²⁴ The likely explanation for an increased risk of developing a cancer and a worsened prognosis from the cancer in higher latitudes is vitamin D deficiency.^{23,24}

The likely mechanism for vitamin D's ability to protect against cancer is that 1-25-OH vitamin D is anti-proliferative and promotes the ordered differentiation of cells. 1-25 OH vitamin D also inhibits telomerase expression, apoptosis, and angiogenesis, which facilitates the spread of tumors.²⁵⁻²⁷ In addition, gene expression associated with DNA repair and maintenance of genome integrity is induced by 1-25-OH vitamin D.²⁵

Colon, breast, ovary, and prostate cancers have been associated with vitamin D deficiency. Increasing vitamin D intake reduces the risk of both breast and colon cancers by 50%, prostate cancer by 49% and ovarian cancer by 36%.²⁸ The level of 25-OH vitamin D, even within the "normal range," has been shown to be inversely proportional to the risk for cancer.²⁹ For

example, there is a linear relationship between 25-OH vitamin D levels and breast cancer up to a 25-OH vitamin D level of 62 ng/mL. Mortality from cancer may also be associated with vitamin D deficiency because the 10-year mortality for breast cancer has been shown to be higher (26% versus 14%) in those with 25-OH-vitamin D levels <30 ng/mL when compared with those with levels >30 ng/mL.^{29,30}

In the National Health and Nutrition Examination Survey (NHANES) men older than age 40 who had an elevated serum parathyroid hormone (PTH) level (assumed to be due to vitamin D deficiency), had an increase in both the free and total prostate specific antigen (PSA) levels, even after adjustment for age, race and 25-OH vitamin D levels.³¹ Indeed, if PTH was above the upper limit of normal, the incidence of an elevated PSA was increased by 43%. In African American males who have a higher incidence and prevalence of prostate cancer, PTH was also higher, indicating that vitamin D deficiency may be an explanation for the higher incidence of prostate cancer in African American men.³¹

Vitamin D and Type 2 Diabetes Mellitus (T2DM)

In the Framingham Offspring Study, those in the highest tertile of 25-OH vitamin D levels had a 40% lower incidence of T2DM than those in the lowest tertile. Furthermore, those in the highest 25-OH vitamin D tertile had significantly lower fasting glucose levels and less insulin resistance as evidenced by lower fasting insulin levels and a 12.7% significantly lower HOMA IR (a measure of insulin resistance) than the lowest tertile.³²

The proposed mechanisms for the improved insulin resistance achieved by correction of low vitamin D levels are:

- (a) that 1-25-OH vitamin D directly stimulates the insulin receptor
- (b) that by regulating extracellular calcium, calcium flux and cytosolic calcium, the uptake of glucose by myocytes and adipocytes is improved
- (c) that by activating the nuclear PPAR delta receptor which regulates free fatty acid metabolism in both the adipocyte and myocyte vitamin D improves insulin resistance and
- (d) through suppressing the activity of the renin-angiotensin-aldosterone system: vitamin D also lowers resistance to the action of insulin.³³

A feature of insulin resistance and the metabolic syndrome is the presence of tissue fat (particularly in the myocardium, liver and voluntary muscle). By CT scan estimation of the quantity of muscle fat it has been shown that there is a strong negative correlation between the fat content of voluntary muscle and vitamin D levels and in those who had vitamin D deficiency, the volume of muscle fat is increased by 23.6%.³⁴ In a study of obese African American adolescents not only was vitamin D deficiency highly prevalent but in those with a 25-OH vitamin D levels below 15 ng/ml insulin

sensitivity was decreased as evidenced by elevated insulin levels on an oral glucose challenge.³⁵ Inflammation which is a key component of the metabolic syndrome, is also increased with vitamin D deficiency due to both an increased generation and effectiveness of inflammatory cytokines.³⁶ In a study of critically ill patients, C-reactive protein levels which are proportional to increases in interleukin-6 levels, were with vitamin D supplementation reduced by more than 25%.³⁷

The majority of insulin-resistant subjects do not develop T2DM because they are able to produce enough insulin to overcome resistance to the action of insulin. Therefore, for T2DM to develop in insulin-resistant subjects less than optimal beta cell function must be present. Beta cell function is usually reduced by 50% at the time of the diagnosis of T2DM, 25% five years after the diagnosis, and 10% or less after ten years, which is when most patients with T2DM need insulin.³⁸ The major factor in the loss of beta cell function in T2DM is accelerated apoptosis, which has been shown to be increased with vitamin D deficiency and decreased when vitamin D deficiency is corrected.³⁹ The mechanism by which vitamin D deficiency causes beta cell dysfunction is by decreasing glucose-stimulated insulin release rather than by decreasing basal insulin secretion.³⁹ This is probably because decreased nuclear 1-25-OH vitamin D levels causes an imbalance between extracellular and cytosolic calcium which decreases calcium flux which in turn inhibits insulin release. In most but not all studies, correction of vitamin D deficiency improves both insulin release and post-prandial glucose levels.³⁹

In prospective studies of vitamin D supplementation the incidence of T2DM has been shown to be reduced. For example, in the Nurse's Health Study those nurses who had a daily intake of at least 800 IU of vitamin D had a 33% lower incidence of T2DM than nurses who had a 200-IU daily intake.⁴⁰ A Finnish study showed similar results, but the relationship with vitamin D intake was attenuated after adjusting for BMI, which is not surprising because the vitamin D deficiency was most likely due to obesity.⁴¹ In another Finnish study men in the highest 25-OH vitamin D quartile had a significantly reduced incidence of T2DM and this association persisted even after multivariate adjustments, including an adjustment for obesity.⁴² A prospective study of the English community of Ely showed that after ten years the initial levels of serum 25-OH vitamin D were inversely associated with the development of insulin resistance and T2DM.⁴³ In NHANES, 25-OH vitamin D levels were inversely associated with HbA1c levels in subjects who did not report having diabetes, which supports a mechanistic link between lower vitamin D levels and the risk of developing T2DM.⁴⁴

A prospective interventional study of vitamin D intake and its association with T2DM was performed as part of the Women's Health Initiative. Supplementation with 400 IU of vitamin D daily had no effect on the development of insulin resistance or T2DM and supplementing with 700 daily units

had no effect on those who had normal glucose tolerance at baseline.⁴⁵ However, if at baseline impaired fasting glucose was present, supplementation with 700 IU of vitamin D daily during the next three years resulted in a decreased development of both insulin resistance and T2DM.⁴⁵ This reduction was similar to the reductions in conversion from impaired glucose tolerance to T2DM that occurred in the Diabetes Prevention Trial with lifestyle modification or metformin.⁴⁶

Pregnant women with pre-existing diabetes are more likely to have vitamin D deficiency.⁴⁷ In addition, with gestational diabetes lower 25-OH vitamin D levels have been documented.^{48,49} In non-diabetic pregnancies the administration of vitamin D in daily doses of 4000 IU compared with daily doses of 2000 or 400 IU has been shown to decrease the incidence of both preterm labor and birth and also to significantly lower the rate of infections that occur during pregnancy.⁵⁰ In the pregnant patient with pre-existing T2DM or gestational diabetes the administration of a single large intravenous dose of 1-25-OH vitamin D has been shown to decrease both insulin resistance and the fasting glucose level.⁵¹

The chronic microvascular complications of diabetes may also be associated with vitamin D deficiency. In NHANES, the prevalence of diabetic nephropathy was significantly increased by 79% in those with vitamin D insufficiency and by 85% in those with vitamin D deficiency.⁵² This association persisted after adjustments for race, gender, hypertension, cholesterol level, cigarette smoking and the use of blockers of the renin-angiotensin system.⁵² Although an inverse relationship between 1-25-OH vitamin D and the severity of diabetic retinopathy has been reported in patients with diabetic nephropathy⁵³ an independent relationship between 25-OH vitamin D levels and diabetic retinopathy has to date not been reported. In addition, while the pain of diabetic neuropathy may be helped with vitamin D replacement, vitamin D deficiency has not been directly associated with diabetic neuropathy.

Conclusion

An association of vitamin D deficiency with autoimmune disease (particularly multiple sclerosis and type 1 diabetes) is well established, and vitamin D supplementation has the potential to avoid the development of type 1 diabetes. Vitamin D deficiency has also been associated with infection and allergy and correction of vitamin D deficiency may improve the manifestations of asthma. Because 1-25-OH-vitamin D is anti-proliferative and promotes differentiation as well as inhibiting apoptosis and angiogenesis, vitamin D deficiency is associated with an increased risk of developing multiple cancers including colon, breast and prostate cancers and is associated with a worsened prognosis from these cancers. Through an effect on insulin resistance and insulin release vitamin D deficiency is associated with type 2 diabetes and may also be associated with diabetic complications.

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Protean Manifestations of Vitamin D Deficiency, Part 3: Association with Cardiovascular Disease and Disorders of the Central and Peripheral Nervous Systems

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Abstract: Vitamin D deficiency is associated with the risk factors of inflammation, insulin resistance and endothelial dysfunction, and left ventricular hypertrophy. As a result there is an increase in cardiovascular events (CVEs) associated with vitamin D deficiency. Vitamin D deficiency itself or secondary hyperparathyroidism or both may be responsible for the increase in CVEs. Correction of vitamin D deficiency may decrease the incidence of CVEs. Vitamin D deficiency is also associated with Alzheimer disease, schizophrenia, depression, and chronic pain and muscle weakness. Vitamin D deficiency is early treated with oral vitamin D supplements which may improve the manifestations of the diseases associated with vitamin D deficiency.

Vitamin D deficiency is common and its manifestations protean. This article reviews the association of vitamin D deficiency with diseases of the cardiovascular and nervous systems.

Vitamin D and Cardiovascular Disease

Vitamin D deficiency is associated with the cardiac risk factors of insulin resistance, hypertension, vascular calcification, inflammation and left ventricular hypertrophy. Vitamin D has also been associated with an increased incidence of congestive heart failure and an increased mortality resulting from the heart failure.¹

Deficiency of vitamin D results in an increased expression of genes that are associated with activation of the renin-angiotensin system and genes that are associated with malfunction of calcium channels.² Therefore, activation of these genes is likely to lead to hypertension, left ventricular hypertrophy and congestive heart failure.

Hyperparathyroidism (whether primary or secondary to vitamin D deficiency) has also been associated with insulin resistance, inflammation, increased carotid intima-medial thick-

ening and cardiac events.³ Levels of vitamin D <18 ng/mL are associated with a 40% increase in cardiac events and in NHANES, an increase in cardiovascular mortality.⁴ Compared with a 25-OH vitamin D level of >15 ng/mL those with a 25-OH vitamin D level <15 ng/mL had a 53% increase in cardiovascular disease and those with a level below 10 ng/mL had an 80% increase.⁴ In older US adults 25-OH vitamin D levels are inversely associated with cardiovascular events and all-cause mortality.⁵ Evidence that vitamin D deficiency is associated with the risk factors of inflammation and endothelial dysfunction was shown in those with lower 25-OH vitamin D levels who had increased asymmetrical dimethyl arginine levels, which is a measure of endothelial dysfunction, and higher C-reactive protein levels, which is a measure of inflammation.⁶

Whether it is increased parathyroid hormone (PTH) levels or simply vitamin D deficiency itself that is responsible for the association of vitamin D deficiency with inflammation and insulin resistance was addressed in 1017 morbidly obese subjects, 68% of whom were judged to have insulin resistance. Although there were no differences in 25-OH-vitamin D levels between the insulin-resistant and non-insulin-resistant subjects, PTH was higher and magnesium levels lower in those with insulin resistance. In fact, patients with PTH levels in the second through fourth quartiles had between a 47% and a 109% increased chance of having insulin resistance even after adjusting for other risk factors.⁷ In this study, 1-25-OH vitamin D, magnesium, and PTH levels were not associated with insulin resistance and PTH levels were associated with the presence of elevated systolic and diastolic blood pressure levels.⁷

When hypertension is accompanied by a deficiency of vitamin D, correction of the vitamin D deficiency may result in improved blood pressure levels. An older controlled study showed that an increase in vitamin D levels, induced by thrice weekly UVB light therapy, resulted in an average drop in systolic blood pressure of 6 mm Hg.⁸ In a Scottish blinded placebo-controlled study performed at the end of winter, vitamin D-deficient individuals were given a single dose of

100,000 U of vitamin D or a placebo. Compared with the placebo group systolic blood pressure dropped by 14 mm Hg and flow-mediated dilatation increased by 2.3% in the group given vitamin D.⁹ In a later study single doses of 100,000 and 200,000 units of vitamin D3 resulted in not only the expected improvement in systolic blood pressure in both groups but also a significant decline in brain natriuretic peptide level with the 200,000 unit but not the 100,000 unit dose, indicating that with the higher dose there was an improvement in left ventricular function.¹⁰

Vitamin D replacement has also been shown to increase total high-density lipoprotein levels mainly due to an increase in the size of the high-density lipoprotein particle.¹¹ The increase in high-density lipoprotein particle size improves reverse cholesterol transportation which has also been shown to improve with vitamin D replacement.¹² Furthermore in an in vitro study which utilized macrophages from type 2 diabetic subjects, the uptake of oxidized low-density lipoprotein and the formation of foam cells was increased when vitamin D was absent. However, in the presence of vitamin D there was activation of the 1-25-OH vitamin D receptor which decreased the uptake of oxidized low-density lipoprotein by the macrophages and foam cell formation.¹³

Surrogate markers of atherosclerosis have also been shown to be increased with both vitamin D deficiency and secondary hyperparathyroidism. With hyperparathyroidism there are increases in carotid stiffness, thickness of carotid plaques, and intima-medial thickness.¹⁴ In fact, for each 10 pg/mL elevation of PTH, carotid stiffness increased by 91%. In subjects with type 2 diabetes mellitus, vitamin D deficiency, with or without hyperparathyroidism, has been shown to be strongly and directly associated with carotid atherosclerosis.¹⁴

In type 2 diabetes mellitus patients, 75% of who are hypertensive, an already high rate of cardiovascular events is further increased with vitamin D deficiency. In the Framingham Heart Study the presence of vitamin D deficiency did not increase cardiac events in non-hypertensive subjects, but in hypertensive subjects with a 25-OH vitamin D level <15 ng/mL, after five years the probability of CV disease was increased by 62% when compared with hypertensive subjects who had vitamin D levels >15 ng/mL. That vitamin D deficiency is not just associated with cardiac events but may be the cause of these events, was shown in a prospective study where after one year subjects who had their vitamin D levels normalized had a 30% lower mortality.¹⁶ In this study the threshold for 25-OH vitamin D above which there was no further benefit in mortality, cardiovascular events or heart failure was 43 ng/mL.¹⁶

Vitamin D deficiency has also been associated with heart failure (HF). In 3299 subjects having coronary angiography and prospectively followed for seven years, low initial 25-OH vitamin D levels were associated with both HF and sudden cardiac death.¹⁷ A recent NHANES study showed that compared with those with a normal 25-OH vitamin D level

(>30 ng/dL), subjects with a level between 20 and 29 ng/dL had twice the frequency of death due to heart failure, whereas those with levels <20 ng/dL had a 3.4-fold increased risk. Indeed those who died of HF were 50% more likely to have a deficiency of vitamin D.¹⁸ In another study, vitamin D deficiency was also associated with a lower exercise tolerance in patients who had systolic HF.¹⁹ It is possible that these negative outcomes are associated with inflammation because HF is an inflammatory state associated with increased levels of inflammatory cytokines, and patients with the highest cytokine levels have the worst prognosis. In HF patients cytokine levels are further increased with vitamin D deficiency and can be reduced with vitamin D replacement.²⁰ HF is also associated with increased activity of the renin-angiotensin aldosterone system which may be further increased with vitamin D deficiency and ameliorated with vitamin D replacement.²¹

The association of vitamin D deficiency with HF may also be because of secondary hyperparathyroidism. Not only is excessive PTH associated with insulin resistance, inflammation, and vascular stiffness but it is also associated with myocardial hypertrophy and fibrosis.^{22,23} Through activation of the 1-25-OH vitamin D nuclear receptor, vitamin D has been shown to suppress myocardial hypertrophy and abrogate the hypercontractability of the myocardium that is observed with diastolic HF.^{24,25} Therefore the association of vitamin D deficiency with HF is likely due to both the effects of vitamin D deficiency and secondary hyperparathyroidism on the myocardium. Based on the available evidence it is likely that HF can be avoided, and with existing HF exercise tolerance can be improved and mortality decreased by correcting the deficiency of vitamin D.

Central Nervous System Manifestations of Vitamin D Deficiency

At least in vitro, vitamin D seems to be neuroprotective.²⁶ In Alzheimer disease, 1-25-OH vitamin D receptors are downregulated and in older adults cognitive function may be inversely related to vitamin D levels as assessed by a simple mini-mental status examination.^{27,28} Higher 25-OH vitamin D levels have also been associated with better memory and information processing, with information processing but not memory persisting after adjustments for other risk factors.²⁹ In another study, cognitive impairment was most pronounced when the 25-OH vitamin D level was <14 ng/dL.³⁰

Low vitamin D levels are associated with chronic fatigue. In a group of head injury patients 80% of those with vitamin D deficiency compared with 40% of those with normal 25-OH vitamin D levels complained of chronic fatigue, especially in the presence of a coexisting sleep disorder.³¹ Vitamin D deficiency may also be associated with an increased risk of developing Parkinson disease because cross-sectional studies of patients with Parkinson disease have shown an association with vitamin D deficiency.³² For example, a cross-sectional study from the southeastern United States showed that the

prevalence of vitamin D deficiency was significantly increased in subjects with parkinsonism compared with controls (55% versus 36%) and even subjects with Alzheimer disease (41%).³³ A Finnish longitudinal cohort study after multiple adjustments found that the risk of developing Parkinson disease was 70% less in those in the top quartile versus those in the bottom quartile of 25-OH vitamin D levels.³²

Although vitamin D deficiency has an association with depression, it is difficult to differentiate whether the vitamin D deficiency is the cause or a consequence. In a large cross-sectional population study, both the presence and the severity of depression were strongly associated with both low vitamin D and high PTH levels.³⁴ As would be expected, vitamin D deficiency often accompanies seasonal affective disorder, for which UVB therapy will improve both the vitamin D level and the depression. In the CHIANTI study of Italian men and women older than age 65 lower vitamin D levels were associated with an increase in depressive symptoms.³⁵

Schizophrenia has a much higher prevalence at the Arctic Circle than it does at the Equator. Poor prenatal care may also be a factor at higher latitudes where the darker-skinned Inuit population need a higher intake of vitamin D. Exposure to low vitamin D intake in utero and in early life has clearly been shown to adversely affect brain development and may be associated with the development of schizophrenia.³⁶ A retrospective study from Finland showed that vitamin D supplementation during the first year of life was associated with a reduced risk of schizophrenia in men but not women.³⁷

Pain, Muscle Weakness, Degenerative Joint Disease, and Vitamin D Deficiency

Both chronic pain and muscle weakness can result from vitamin D deficiency. 25-OH vitamin D levels <12 ng/dL have been associated with severe pain and muscle weakness, which have both rapidly resolved with vitamin D replacement.^{38,39} It has been estimated that 90% of non-fibromyalgia-related muscle pain may be due to vitamin D deficiency and also that the pain associated with diabetic neuropathy can be alleviated when vitamin D deficiency is corrected.⁴⁰ In contrast, pain associated with fibromyalgia has never been shown to be associated with vitamin D deficiency nor to be improved with vitamin D supplementation.⁴¹ US servicemen returning from Iraq and Afghanistan often have musculoskeletal pain due to demineralized bone hydration, expanding and stretching the periosteum. Vitamin D deficiency due to lack of sun exposure with battle dress is responsible for these findings, and correction of vitamin D deficiency results in a rapid resolution of the musculoskeletal pain.³⁹

Improvement in neuropathic pain with the correction of vitamin D deficiency should not be surprising because vitamin D through its receptor modulates neuronal differentiation, growth, and function.⁴² A deficiency of vitamin D impairs nociceptor function, worsens nerve damage, and lowers the pain threshold.⁴³ Neuromuscular coordination also improves

with correction of vitamin D deficiency as evidenced by the decreased frequency of falls in elderly subjects.⁴⁴

With degenerative joint disease, correction of vitamin D deficiency may result in relief of pain due to not only elevation of the pain threshold but also an effect on the underlying disease. A study of men with a 25-OH vitamin D levels between 15 and 30 ng/mL compared with those with a level >30 ng/dL showed a 2.19% increased prevalence of osteoarthritis of the hip. A possible reason for the association of vitamin D deficiency and degenerative joint disease is that the Wnt pathway, from which chemicals that are important in cartilage formation are generated, is regulated by 1-25-OH vitamin D. In addition, chondrocyte metabolism is adversely affected by a deficiency of vitamin D. Vitamin D also regulates the ratio of RANKL to osteoprotegerin so that a deficiency of vitamin D will result in a deterioration in the formation and repair of the articular bone.⁴⁵

A common painful situation is statin-induced myalgia, myositis, or occasionally rhabdomyolysis. Statin-induced myopathies most commonly occur with statins that are fat-soluble and/or inhibit the hepatic enzyme CYP3A4. The clinical experience has been that myopathies associated with statin therapy can often be resolved by correcting vitamin D deficiency and a recent single case study reported resolution of statin myalgias with vitamin D replacement.⁴⁶ However, a larger retrospective observational study showed that vitamin D levels were significantly lower in patients with myalgias and that in myalgic subjects correction of vitamin D deficiency resulted in the resolution of statin-induced myalgias in 92%.⁴⁷ An Australian prospective study found that four of six patients with statin-induced myalgias and vitamin D deficiency following correction of this deficiency on rechallenge with the same statin were statin tolerant.⁴⁸ However, in a retrospective analysis, vitamin D levels did not show an association with myalgias in the Treating to New Targets study, in which subjects were treated with either simvastatin 80 mg or atorvastatin 10 mg.⁴⁹

Treating Vitamin D Deficiency

Nutritionally, vitamin D can be derived from dairy foods and fatty fish such as salmon, mackerel, and tuna. However, 20 minutes of sunshine or five to seven minutes in a tanning bed generate five times more vitamin D3 than that obtained from eating 3 ½ ounces of salmon.⁵⁰ Exposure to sunlight also increases the risk of skin malignancies, so that various recommendations for the prudent use of sunscreen such as leaving the arms and legs free of sunscreen or delaying use of sunscreen for 20 minutes after exposure have been advocated. However, oral supplementation with either vitamin D2 or vitamin D3 is probably a safer but less physiological way to normalize vitamin D levels. Proponents of cholecalciferol (vitamin D3) claim that D3 is 3- to 10-fold more effective in raising 25-OH vitamin D levels, has a higher affinity for the vitamin D binding protein, results in more 25-OH vitamin D generation, and has a greater affinity for the vitamin D

receptor. Proponents of D3 also claim that vitamin D3 but not vitamin D2 (ergocalciferol, a synthetic vitamin D product) has been shown to prevent bone fractures. However, most clinicians believe that there is little if any difference between supplementation with D3 and D2 and because D2 is more readily available, it is the most prescribed vitamin D replacement therapy.⁵¹

When vitamin D deficiency is diagnosed, doses of 50,000 to 100,000 U weekly dependent upon the 25-OH vitamin D level are recommended. After three months if the 25-OH vitamin D level is in the sufficiency range, the weekly dose that resulted in the correction of the 25-OH vitamin D level should be administered on a monthly basis or more frequently depending on monitoring of 25-OH vitamin D levels.^{1,51} In severe cases of vitamin D deficiency such as those that occur after gastric bypass surgery, higher and more frequently administered doses may be necessary.

Conclusion

Vitamin D deficiency is common, easily detected, and easily treated. Vitamin D deficiency is also associated with insulin resistance, type 2 diabetes, cardiovascular disease, central and peripheral nervous system dysfunction and chronic pain syndromes. Whether early recognition and correction of vitamin D deficiency may prevent reverse or ameliorate these diseases has not been established or even assessed. As a result, the Institute of Medicine reported that a 25-OH vitamin D level is adequate for bone strength and that it was not clear whether higher levels are beneficial for other medical conditions because studies are based on associations and do not prove causality. It was also stated that a level >50 ng/mL had the potential for adverse health effects (hypercalciuria and nephrolithiasis) and that a level between 20 and 50 ng/mL is safe and effective for bone health. However, particularly with cardiovascular disease, outcomes of vitamin D replacement therapy have been encouraging. Research into the prevention and improvement of conditions associated with vitamin D deficiency is urgently needed. Should these outcome studies show a benefit from correcting vitamin D deficiency, it will then be proven that screening for vitamin D deficiency is both beneficial and cost-effective.

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