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Review Article

The Physiological Consequences of Hypovitaminosis D: Associated Diseases

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During the industrial revolution in the United States, speculations arose surrounding ultraviolet radiation and its inverse relationship to the alarmingly increasing prevalence of rickets, a bone disease in children that we now know is caused by a lack of vitamin D. However, prior to the 20th century, it was nearly impossible to simply identify biological forms of vitamins or hormones (Holick, 2010). It was inconceivable to set forth a list of dietary essentials and their roles in the human body. With the aid of modern technology, the ability to ascertain vitamin D's chemical form and origins became a reality. Today, a large fraction of the field of endocrine research aims to find links between vitamin D and diseases. The purpose of this paper is to list some of the associated ailments that transpire alongside inadequate levels of vitamin D, and in turn, emphasize the importance of supplementation to prevent such occurrences.

Keywords: Vitamin D, Hypovitaminosis D

Compared to other well-known vitamins essential to our health, vitamin D is unique in the sources it derives from and its biosynthesis within the human body. Ergocalciferol, or vitamin D_2, is found in plants and is classified as a phytonutrient, a form of chemical that helps protect plants from threats such as germs and bugs. Ergosterol, a type of steroid alcohol, occurs naturally in members of the fungi kingdom. Ergosterol is also called provitamin D_2, as it gets converted into ergocalciferol upon exposure to UV radiation. Cell membranes of mushrooms, in particular, are abundant in ergosterols, which can account for their reliability as a source of vitamin D_2. Processed food and supplement manufacturers often take advantage of mushrooms' natural concentrations of ergosterols and elicit extensive irradiation in mass quantities. However, the most biologically active form of vitamin D in humans that is preferable is not ergocalciferol, but cholecalciferol, otherwise known as vitamin D_3. Cholecalciferol is considered to be superior in regards to its absorbability and efficacy in humans. Research shows that ergocalciferol must be given in much higher doses than cholecalciferol to achieve similar metabolic benefits (Houghton & Vieth, 2006). The study goes on to state that, "…ergocalciferol should not be regarded as a nutrient suitable for supplementation or fortification." In a similar study on the potency distinction between ergocalciferol and cholecalciferol, it was concluded that vitamin D_3 is approximately 87% more potent in raising and maintaining blood 25(OH)D concentrations and produces a 2 to 3-fold greater storage of vitamin D than with the equivalent amount of vitamin D_2 (Heaney et al., 2010).

As ergosterols function in fungus cells to form ergocalciferol, 7-dehydrocholesterol similarly absorbs UV radiation in human skin cells to form cholecalciferol. Cholecalciferol is not yet active and does not implement significant biological activity. Within the liver, the enzyme 25-hydroxylase introduces a hydroxyl group [-OH] to form 25-hydroxycholecalciferol, or calcidiol. Calcidiol serves as a substrate for 1-alpha-hydroxylases, which are enzymes found in the kidneys. The result is the biologically active form of vitamin D, 1,25-dihydroxycholecalciferol or calcitriol. (Bowen, 2011).

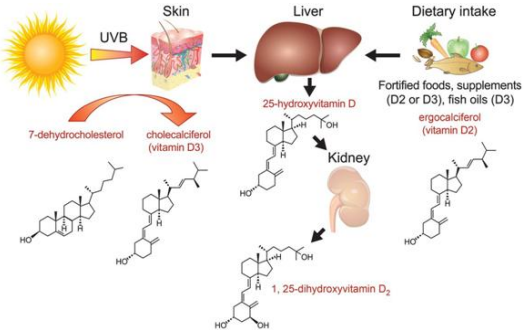

Figure 1: Vitamin D biosynthesis and metabolism (Ibhar, Patel, Tangpricha, 2013).

Vitamin D, now in its active form of calcitriol, carries out various physiologic effects on the body. Although commonly accepted as the nutrient vital to our bone health, calcitriol carries out this function indirectly as it facilitates calcium and phosphorus absorption from the intestines to the blood. Calcium is the most abundant mineral found in the body and acts to keep our bones and teeth strong as well as perform roles in but not limited to: blood clotting, muscle contraction, nerve signal transmission, and fertilization during sexual reproduction (Houtkooper & Farrell, 2011). Calcium molecules also interact with sodium, potassium, and magnesium to regulate blood pressure and water balance. As such, low levels of vitamin D can induce skeletal system disorders as well as compromise various functions of the circulatory, muscular, nervous, and reproductive systems.

Vitamin D levels in the blood are measured by the widely accepted 25-hydroxyvitamin D, or 25(OH)D test. Fasting for four to eight hours before the blood test is highly recommended. The Endocrine Society characterizes hypovitaminosis D, or low levels of vitamin D, as a 25(OH)D level of below 20 ng/mL of blood serum obtained. The National Institutes of Health has concluded that a level of 20 ng/mL or above is adequate for bone health but levels greater than 30 ng/mL do not create any further benefits.

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Table 1: (Ross et al., 2011). 25-hydroxyvitamin D levels and health status.

Serum 25(OH)D concentrations (ng/mL)	Health status
<12	Vitamin D deficiency. Causes rickets in children and osteomalacia in adults
12-20	Inadequate for bone and overall health
=20	Adequate for bone and overall health
>50	Potentially adverse effects

Low levels of vitamin D can be caused by a variety of factors, the most common of which is inadequate exposure to sunlight. The "sunshine" vitamin as it is sometimes called, its deficiency is more common in those who are often housebound, live among northern latitudes, or have darker skin. Pigmentation, created by the pigment, melanin, is determined by the concentration of melanocytes (cells that produce melanin) in the epidermis of the skin. Ethnic groups that have historically been consistently exposed to UV radiation have increased synthesis of melanin, which acts to help block out harmful rays and prevent cancer (Brenner & Hearing, 2008).

Besides sun exposure due to varying lifestyles or location of residence and melanocyte concentration in the skin, nutritional and digestive system factors also contribute to vitamin D levels in the body. As previously mentioned, vitamin D_2 is commonly found in plants and mushrooms. The more potent vitamin D_3 is found in fatty fish, egg yolks, cheese, and most abundantly in cod liver oil, a teaspoon of which provides upwards of 300% of the daily value of vitamin D.

Satisfying the recommended daily intake of vitamin D (600 IU/day) may still leave 25(OH)D blood concentrations unchanged if organs of the digestive tract are not fully functioning. A healthy digestive tract is vital; stomach juices, pancreatic secretions, bile from the liver, and the quality of the walls of the small intestine contribute to nutrient absorption (Simon, 2011). Digestive system disorders, such as Crohn's disease, are often associated with vitamin D deficiency, which will be discussed later. Also, renal disease often causes low serum levels of 25(OH)D. According to a study on chronic kidney disease (CKD), patients inflicted with CKD have an exceptionally high rate of severe vitamin D deficiency, marked by the renal inability to convert calcidiol into the active form of calcitriol (Williams et al., 2009).

As vitamin D facilitates dietary calcium absorption and promotes bone health, severe deficiency seen among children often results in rickets. Rickets is a condition that causes softening and weakening of the bones and is commonly diagnosed between the ages of 3 months and 3 years, during the time of rapid growth. The analogous condition in adults is called osteomalacia; which, like rickets, is accompanied by a variety of symptoms such as pain, weakness, susceptibility to fractures, bone disfigurement, teeth defects, abnormal heart rhythms, and spasms of the limbs. However, unlike rickets, osteomalacia is easily treated and symptoms are reversed with adequate vitamin D and calcium supplementation. For children inflicted with rickets, supplementation cures the problem within 6 months but the previous skeletal deformities may remain (Margolis, 2014).

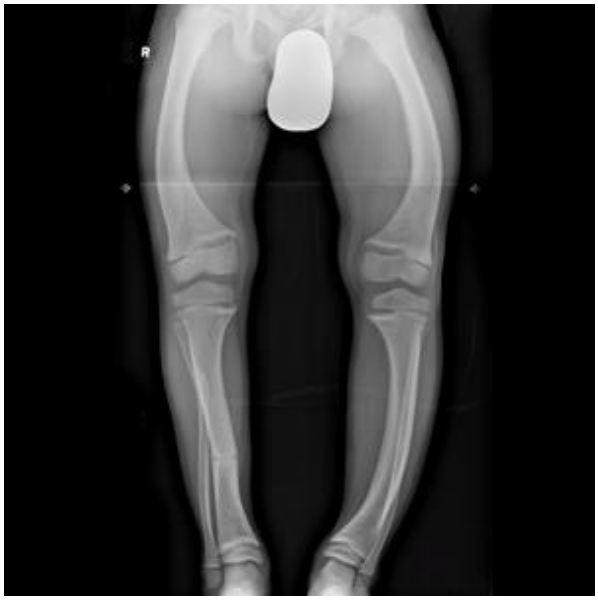

Figure 2: Bowed legs seen in x-ray of child with rickets (Ott, 2016).

The importance of the role of vitamin D in the growth and maintenance of the human skeletal system has long been established worldwide and supplementation is encouraged in order to keep our bones strong and healthy. However, a connection between vitamin D and our nervous system was made fairly recently. Research has yielded a significantly furthered understanding of the neuroprotective effects of vitamin D. Among the disorders associated with hypovitaminosis D are Parkinson's disease, epilepsy, schizophrenia, multiple sclerosis, and Alzheimer's disease, the last two of which will be discussed shortly. The interest in the involvement of vitamin D in the nervous system was first sparked by the discovery of the concentrations of 1-alphpa-hydroxylases (enzymes that catalyze the conversion of calcidiol into calcitriol) in the brain (Wrzosek et al., 2013). Along with these enzymes, vitamin D receptors were also found mainly in the brain's hypothalamus, dopaminergic neurons (source of dopamine), and within membranes of microglia (immune cells of the central nervous system). The hypothalamus is the section of the brain responsible for the production and inhibition of essential hormones, which governs physiologic functions such as body temperature regulation, thirst, hunger, sleep, and our moods (Dougherty, 2015). Dopamine is a highly essential neurotransmitter that carries out various roles in movement, memory, cognitive function, problem solving, and pleasure. Microglia are typically oval-shaped cells with long cytoplasmic projections that allow for the clearing of cellular debris and dead neurons by the means of phagocytosis (cell-eating) (Rogers, 2016). Thus, due to vitamin D's interaction with the receptors on these cells, its deficiency negatively impacts their intracellular metabolic pathways, ultimately affecting the cells' abilities to carry out their crucial functions.

Multiple sclerosis (MS) is a disease of the brain and the spinal cord, in which one's own immune system attacks the myelin sheath of the nerve fibers. Myelin is a fatty white substance that functions to increase the speed of nerve

impulses by electrically insulating the axons of neurons. The degeneration of myelin sheath results in the slowing down or blockage of signal transmission, leading to progressively disabling symptoms such as: tingling and numbness; pain and spasms; fatigue and weakness; balance problems and dizziness; bladder, bowel, and sexual dysfunction; and cognitive problems (Wilson, 2015). A research study of vitamin D's role in the prevention and treatment of MS has concluded that with vitamin D's neuroprotective factors and anti-inflammatory capacities, a higher 25(OH)D serum concentration has been shown to be associated with favorable and improving disease courses (Dörr et al., 2013). In a recent clinical study composed of participants inflicted with MS (all of whom were given the same commonly prescribed medication), the objective was to determine whether their differing, initial 25(OH)D levels can allow for the accurate prediction of their disease activity and prognoses. The results were explicit and researchers' predictions were precise; higher levels of vitamin D were associated with the group of patients characterized by a gradually reducing MS activity and a slower rate of progression than those with lower levels, often characterized by higher relapse rates, increasing loss in brain volume, and increased disability (Ascherio et al., 2014). This allowed for the conclusion that vitamin D aids in the prevention of the growth of new lesions (damaged areas) along with the ordinarily prescribed immunosuppressive drugs. Rather than the drugs alone, combining them with vitamin D supplementation has shown to be far more effective in the treatment of multiple sclerosis.

While multiple sclerosis causes demyelination of the central nervous system, Alzheimer's disease (AD) results in progressive neurodegeneration, or neuron death, and is the most common form of dementia and cognitive impairment in the aging population. As brain size shrinks over time, the fewer concentration of neurons and neural connections induces a substantial loss in cognitive function and memory. Interestingly, both MS and AD are caused by ongoing inflammation in the brain and spinal cord. Vitamin D's anti-inflammatory capacities allowing for the betterment in MS patients suggested applying

Score	Interpretation
24 - 30	"Normal" range
20 - 23	Mild cognitive impairment or possible early-stage/ mild Alzheimer's disease
10 - 19	Middle-stage/moderate Alzheimer's disease
0 - 9	Late-stage/severe Alzheimer's disease

Figure 3: Mini Mental State Examiniation (MMSE) (n.d.).

the same concept in elderly adults diagnosed with AD. Gangwar et al. (2015) composed a clinical study surrounding this concept; 80 subjects were enrolled based on confirmed statuses of vitamin D deficiency and Mini Mental State Examination (MMSE) scores of less than 24. The MMSE is a 30-point questionnaire often used in research and clinical settings to measure cognitive impairment and mental status (Crum et al., 2016). The 80 participants were equally divided into group A and group B; the experimental and control group, respectively. Subjects in group A were given vitamin D supplementation to correct their deficiency according to their body mass index, while group B underwent no change. A significant increase in MMSE score was observed in the span of 6 months in only group A, which concluded that vitamin D supplementation lead to improvement in cognitive performance in subjects with senile dementia.

Besides aiding in the prevention of skeletal and nervous system disorders, studies have also displayed vitamin D's roles in maintenance of a healthy digestive system. Inflammatory bowel disease (IBD) is a group of disorders that causes chronic inflammation of the digestive tract. Symptoms include but are not limited to: persistent diarrhea; severe abdominal cramping and pain; fatigue; rectal bleeding; loss of appetite; and weight loss. Crohn's disease (CD) in particular, one of the main types of IBD, can harm any part of the gastrointestinal tract from the mouth to the anus although mostly affecting the ileum (the end of the small intestine) and the beginning of the colon. Pathogenesis, or development, of CD is believed to involve conflictions in innate immunity, a combination of bodily defense mechanisms against nonspecific pathogens that can potentially cause infection. Vitamin D receptors are not only present in neuronal cells but in immune cells as well, which is suggestive of its immunological roles (Prietl et al., 2013). According to a clinical study surrounding vitamin D's contribution to immunity and the autoimmune elements of CD, it was discovered that there were significant associations between dietary and supplemental vitamin D and the quality of life in patients diagnosed with mild to moderate CD. Crohn's disease Activity Index, or CDAI, is a tool used to calculate the condition and its severity in patients inflicted with CD in order to determine dosage and kind of medicine. In this particular study, the CDAI scores were used to observe if patients' quality of life improved following vitamin D supplementation. Results were staggering; the mean CDAI score dropped 112±81 points from 230±74 to 118±66 (Yang et al., 2013). To understand the significance, it is known that remission of CD is defined as a CDAI score below 150 and was explicitly shown in the patients post-experiment with a more positive quality-of-life score. Many researchers aim to create new CD medications that prompt decreases in CDAI scores of at least 70 points; and this study imparts that it may be helpful to include vitamin D in the development of such drugs to achieve that goal.

Such emergence of vitamin D's previously unknown physiological roles in the body has encouraged researchers to also observe its roles in the pregnant woman and fetus. According to the Royal College of Obstetricians and Gynecologists in the United Kingdom, gestational complications due to hypovitaminosis D include increased risks and incidences of miscarriage, need for Caesarean sections, and preeclampsia. Negative outcomes and impact on the fetus include low birthweight and impaired growth (Robinson et al., 2014).

Miscarriage is the most common type of pregnancy loss; 40 out of every 100 pregnancies end in the spontaneous death of the fetus (White, 2014). Many factors can contribute to facilitate this devastating outcome of pregnancy; some of which can be identified in order to lessen its incidence in the general population, including maternal 25(OH)D levels. A study in Denmark was conducted in order to determine whether or not 25(OH)D levels were indeed modifiable risk

factors for first-trimester (week 1-12) miscarriage (Andersen et al., 2015). Vitamin D levels were obtained from 1,684 pregnant women in the early stages of their pregnancy and were then closely monitored in the event that miscarriage occurred. The fraction of the participants who had experienced a miscarriage prior to the twelfth-week mark had lower 25(OH)D levels than the women who had not. Consequently, it was safe to suggest that women with 25(OH)D levels less than 20ng/mL were 2.5 times more likely to miscarry than the women with levels above; and that ultimately, vitamin D plays a notable role in the growth and development of the fetus.

If the fetus is able to sustain oneself despite unfavorable vitamin D levels throughout the length of a full-term pregnancy, the likelihood of the need for a Cesarean delivery (c-section) remains higher than average, regardless. As it has been shown that vitamin D is highly influential in promoting healthy fetal growth, safe and conventional delivery methods may also be compromised if the mother exhibits inadequate levels of vitamin D. One of the many reasons for performing c-sections is stalled labor. Stalled labor occurs when uterine contractions are too weak in order to expel the baby in an efficient manner; thus the recommendation to undergo a c-section by the medical personnel to prevent further distress on both the mother and the baby (Cirino, 2016). As the uterus is composed primarily of smooth muscle that functions to yield strong labor contractions, researchers have attempted to draw a connection between uterine dysfunction during labor and vitamin D deficiency. From the years 2005 to 2007, 253 births were observed at an urban teaching hospital located in Boston, Massachusetts (Merewood et al., 2008). Along the duration of the study, an analysis was continually reinforced: women with low 25(OH)D levels were almost four times as likely to have undergone a c-section compared to those with normal levels. Countless elements, such as liability concerns, can instigate a medical team to resort to such a drastic procedure that entails increased risks of infection and a significantly extended recovery time. However, to justify and validate their findings despite the possible contingencies, Merewood et al. disclosed an unfrequented fact that muscle cells contain vitamin D receptors, as well as the well-established fact that calcium, as previously discussed, plays a role in muscle contraction and its serum levels are regulated by vitamin D; implicating poor muscular function is symptomatic of vitamin D deficiency.

Miscarriage, c-sections, and natural vaginal births are possible denouements to a fetus's journey in the womb. Besides the potential outcomes, pregnancy in the general months can spark a wide array of changes in the mother. Some of the common changes a woman may experience during pregnancy include an increased resting heart rate, increased respiratory rate, recurrent heartburns, and the frequent need to urinate. Such alterations are normal as the body makes adjustments to accommodate the baby. A less common condition associated with pregnancy is preeclampsia, a complication marked by high blood pressure and the presence of protein in urine, or proteinuria. The kidneys function to filter out waste products and excess fluid from the body, but proteinuria may indicate renal damage since proteins are essential and should have been retained. In a study designed to assess the effect of initial 25(OH)D levels on the risk of preeclampsia, it was found that adjusted 25(OH)D concentrations in early pregnancy were 15% lower in women who subsequently developed preeclampsia compared with controls (Bodnar et al., 2007). Although many studies have explored the correlation between reduced maternal 25(OH)D levels and preeclampsia, this particular study was the first to enroll women prior to their onset of clinical symptoms, demonstrating the researchers' initial hypothesis to be correct.

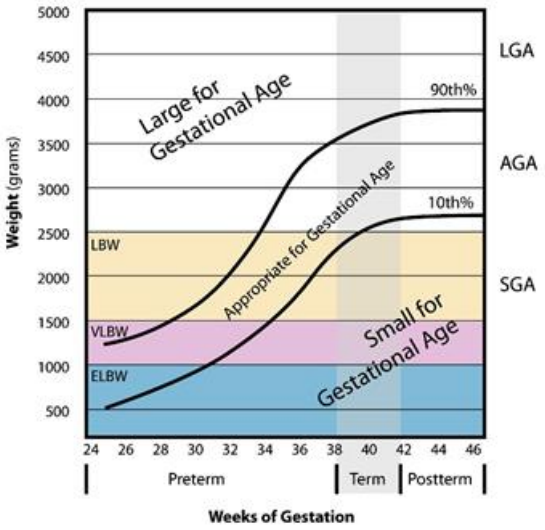

Figure 4: SGA accounts for a birthweight that is below the 10th percentile (Sacks, 2015).

While hypovitaminosis D can be an underlying cause of maternal preeclampsia, it can also increase the risk of a "small for gestational age" (SGA) baby. SGA babies are characterized to be smaller or less developed than what's considered to be optimal for the baby's gender and gestational age (Sacks, 2015). Intrauterine growth restriction (IUGR) manifests for SGA and refers to the poor growth of the fetus in the uterus during gestational periods. SGA babies often display problematic traits such as polycythemia (excess red blood cells), inability to regulate body temperature, hypoglycemia (low blood sugar), and low Apgar scores (Trevino, 2016). Within minutes of post-delivery, the Apgar score rates the baby's breathing efforts, heart rate, muscle tone, reflexes, and skin color on a scale of one through ten (Kaneshiro, 2014). Since the established risk factor for both SGA and IUGR is malnutrition on behalf the mother, attempts have been made to exemplify the lack of vitamin D as part of this risk factor. In a study composed of an entirely Chinese population with no known underlying factors (e.g. cigarette-smoking, alcohol consumption, history of preeclampsia, etc.), a positive correlation was revealed between birthweight and 25(OH)D levels (Chen, 2015). Furthermore, this study included the surmise that risks of infant mornidity-related phenomena such as sudden infant death syndrome, commonly

Table 2: Maternal 25(OH)D levels during pregnancy and the corresponding birthweight with 95% confidence intervals noted. A positive correlation is displayed; higher concentrations of serum 25(OH)D is associated with greater birth weights. (Chen, 2015).

Serum 25(OH)D, ng/mL	n	Cumulative %	Birth Weight, g (95%CI)
<10	46	1.26	2430.1 (2249.9, 2610.3)
10–14	303	9.54	3095.8 (3049.6, 3142.1)
15–19	1056	38.41	3244.1 (3218.8, 3269.4)
20–24	545	53.31	3292.5 (3261.6, 3323.5)
25–29	744	73.65	3499.9 (3472.0, 3527.7)
30–34	488	86.99	3614.2 (3577.6, 3650.7)
35–39	273	94.45	3789.5 (3743.8, 3835.2)
40–44	99	97.16	3804.2 (3729.3, 3879.1)
45–49	49	98.50	3779.0 (3659.0, 3899.0)
≥50	55	100.00	3793.5 (3685.4, 3901.6)

known as SIDS, is increased along with maternal hypovitaminosis D and SGA; however, this requires further research. As daunting as SIDS is as it is marked by unforeseen and unexplained death of the newborn, it has affected nearly 1,500 in the year of 2014 alone (Centers for Disease Control, 2016). As much as efforts have been made to investigate why and how SIDS occurs, there is no logical and ethical way to conduct a research; families can only decrease their chances of such tribulation by implementing supplementation.

Discussion

As clinical studies and general scientific findings have shown over the decades, vitamin D has a stellar impact on health and maintenance of physiology within the body. Not too long ago would the "sunshine vitamin" be only reputable for maintenance of bone health. Despite its simplistic biological nature defined by a 4-carbon ring backbone, vitamin D unleashes a multitudinous list of effects on the human body. Its primary form of 7-dehydrocholesterol provided by the sun is waxed and waned by various organs to become the functional form of calcitriol. Calcitriol then goes on to bind onto vitamin D receptors, found in virtually every cell and tissue within the body. In fact, it is approximated that an upwards of 2,000 genetic sequences are either directly or indirectly regulated by vitamin D (Holick, 2010). Advancements in scientific know-how has allowed for studies surrounding diseases such as AD, rickets, osteoporosis, and preeclampsia during pregnancy; and they have successfully delineated vitamin D's effect on various functional systems. Its deficiency wreaks disorders of the bones, inflicting physical impairment. It can exacerbate existing conditions such as the debilitating brain and spinal cord disorder of MS. Increased concentrations of vitamin D within the blood supply of intestinal linings allows for readily and efficient dietary calcium absorption and alleviates flare-ups of IBD.

It is safe for children and adults of all ages, as well as pregnant women, to implement the practice of scrutinizing nutritional intake. Applied on a global scale, it would result in a significant decline in rates of illness and subsequent mortalities. Vitamin D deficiency is common; and the lack of awareness concerning the effects of hypovitaminosis D allows for increased occurrences of daily pain and fatigue, dwindling the quality of everyday life in a vast majority of the world. Although many elements can contribute to this widespread pandemic of hypovitaminosis D such as environmental factors and one's skin color, studies have consistently proven and stressed the importance of vitamin D. Despite such circumstances, we should continue to enlighten the population of the boundless benefits of vitamin D.

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