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Vitamin D3: Clinical Overview and Applications from 10 Years of Research Reviews

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This review addresses research over the last decade on vitamin D status in the global pediatric population and advancements to the understanding of extra-skeletal benefits of vitamin D. Research over the last decade reveals the majority of infants and children in Europe, Asia, and the United States do not meet standards for sufficient vitamin D levels. Diet and cutaneous synthesis are not consistently reliable to maintain healthy vitamin D levels, especially in winter months at high latitudes. Recent studies which unveil the scope of vitamin D as a vitamin and steroid hormone stretches far beyond the benefits to skeletal health and calcium homeostasis. Receptors for vitamin D have been found throughout the body and brain, suggesting numerous essential and vital functions for vitamin D. The last decade of scientific studies has provided associations between clinical disorders afflicting the pediatric population and low vitamin D levels. Insufficiencies have been linked to various health conditions including asthma, allergies, dermatitis and autism. Vitamin D supplementation has been used therapeutically to significantly reduce seizure occurrence in epileptics, as well as symptoms of autism in children. **Conclusion** – The high prevalence of vitamin D insufficiency around the world and the studied conditions associated with insufficiencies, as well as the positive outcome of supplementation therapy, stress the importance of maintaining adequate vitamin D levels. Supplementation with vitamin D3 is the most advisable way to ensure adequate amounts daily.

Introduction

The intent of this article is to provide the reader with awareness of the significance of vitamin D for a growing child, and the present state of insufficiencies. The scope of this paper includes the role of vitamin D in child development, the prevalence of deficiencies among youth worldwide, and the many clinical disorders associated with these inadequate levels. This paper reviews supporting research over the last decade on vitamin D including ways in which insufficiencies and associated detrimental health effects in children may be ameliorated, along with avenues for further research.

The methods of this review involved primarily searching for vitamin D related articles on the United States National Library of Medicine's databases, predominantly PubMed. A quick search on PubMed for "vitamin D" in the last 10 years (2008-2018) yielded over 35,000 articles from studies world-wide. The previous decade (1998-2008) yielded 16,730. This last decade has seen a greater than two-fold increase in articles on vitamin D. This wealth of research is enlightening physicians around the world on the full significance and importance that vitamin D3 exerts on every major organ system within the human body and brain. This article aims to investigate the last decade worth of research as it pertains to vitamin D3 in the pediatric population, concentrating on areas of new interest. This article intends to highlight, for researchers and clinicians, the role of vitamin D3 as it contributes to early development. Unless otherwise noted, vitamin D shall henceforth refer to the form vitamin D3, cholecalciferol.

Childhood is the most critical period for development after birth. A lack of nutrients during the pre-pubescent stage may lead to the improper formation of body systems such as the skeletal system. This has been shown to result in adverse life-long effects on health. As one of many nutrients necessary for development during childhood, vitamin D is known to be crucial to proper bone formation, regulation of calcium levels, and proper immune response (1).

The recent interest in the role of vitamin D during childhood development has fueled numerous studies over the last decade that provide valuable information. Therefore, the aim of this work is to present the reader with the latest research findings on extra-skeletal benefits of vitamin D3 and clinical applications in the global pediatric population.

Historical Role

In its most classical sense, vitamin D is known for its importance in proper bone formation and growth, occurring largely during childhood, and regulation of calcium levels. Vitamin D is necessary for the body's absorption of calcium obtained from diet. Subsequently, calcium is deposited in the bone, creating a strong mineral-dense skeleton for a growing child. It has been shown that children with vitamin D deficiency can develop nutritional rickets, a malformation of the skeleton characterized by bowed legs. Malformation of the skeleton is typically preventable during childhood with adequate vitamin D and calcium intake.

Intake

Vitamin D is obtained three ways: the skin's exposure to sun, consumption of vitamin D rich foods such as fish, and supplementation (2). During winter months in nations above the 50^{th} parallel (50° N latitude), which includes parts of European countries such as Germany, Poland, France, and Belgium, sun exposure alone is not sufficient to maintain adequate vitamin D synthesis (3). Relying solely on diet for vitamin D intake is not encouraged because few foods are vitamin D rich. Among the foods rich in vitamin D, fish are one of the highest; not all fish are safe to eat however, as many contain harmful substances known as dioxins (4). Dioxins, toxic by-products from sources such as pesticides, will accumulate in fatty tissue. This can have detrimental effects on a child's development. Given these limitations of sun exposure and diet, regular vitamin D supplementation is advised.

Physiology

Upon absorption, vitamin D must be converted to the active form 1,25-dihydroxyvitamin D in order to be utilized in the body. The form of vitamin D in the body that has a higher affinity for the vitamin D binding protein is vitamin D3 or cholecalciferol (5), which is obtained through diet and cutaneous synthesis. This version is inactive until the liver and subsequently the kidneys, using tissue-specific enzymes, convert cholecalciferol into 25-hydroxyvitamin D through action of the liver and then to 1,25-dihydroxyvitamin D through action of the kidneys. 1,25-dihydroxyvitamin D is considered the active hydroxylated form calcitriol.

Clinical Measurements

Vitamin D levels are measured clinically as the concentration of the inactive form 25-hydroxyvitamin D in blood serum. This form is the most abundant in circulation and has become the standard determinant in vitamin D status as it represents the vitamin D from both diet and sun exposure (1, 6). Four main categories of vitamin D status acknowledged are: Deficient (<20 ng/ml or 50 nmol/L), insufficient (<30 ng/ml or 75 nmol/L), sufficient (≥30 ng/ml or ≥75 nmol/L), and toxic (>150-200 ng/ml or >375-500 nmol/L) (7). Levels considered deficient are too low to ensure the prevention of rickets (2, 7). Levels considered insufficient are below concentrations shown to maximally suppress Parathyroid Hormone (7, 8). Levels deemed sufficient ensure prevention of rickets for the majority of the population (97.5%) as well as maximal suppression of Parathyroid Hormone (7). Toxicity has not been documented as an issue less than 150 ng/ml for the majority of the population (7, 8).

Prevalence of Deficiencies

In recent years we have seen a rise in vitamin D deficiency that concerns clinicians and parents alike. It is thought to be partly due to the decrease in time spent outdoors in direct sun (9). Even when out in the sun, many children are covered in sunscreen. More than half of the current pediatric population in the U.S. is classified as having insufficient vitamin D levels (10). These insufficiencies are not restricted to the U.S. alone, as low levels of vitamin D over the last decade have been documented in children throughout Europe and Asia (11, 12). In Europe as of 2016, only 50% of schoolchildren were vitamin D sufficient (≥30 ng/ml) (11). In 2014 in Wenzhou, southeastern China a study conducted found that over 50% of adolescents were vitamin D deficient (13). A study conducted on 380 healthy infants and toddlers in the U.S., found that over half of the participants had levels of vitamin D <50nmol/L (20 ng/ml) (14). The authors advocate for all breastfed infants to receive vitamin D supplementation.

Supplementation and Dosing

In 2008, the American Academy of Pediatrics doubled the recommended daily intake of vitamin D3 for infants, children and adolescents from 200 IU (5 mcg) to 400 IU (10 mcg). By 2014, the recommendations increased further to 600 IU (15 mcg) for children 1 to 18 years old (6). According to a 2010 study funded by the Nation Institute for Health (US), the majority of infants regardless of being breastfed or formula fed, did not obtain the recommended daily intake for vitamin D (15). They suggest all infants should supplement with vitamin D3.

Basic Daily Requirements

The amount of vitamin D3 that is recommended daily is the amount sufficient for most children (97.5%) to prevent rickets and maintain calcium levels (2). According to the Institute of Medicine (US) the adequate intake established for infants 0-12 months is 400 IU (10 mcg). The amount daily suggested for children 1 and older is 600 IU (15 mcg). The Endocrine Society Committee suggests children at risk for vitamin D deficiency, such as children with dark skin pigmentation or breast-fed infants not already supplementing with vitamin D, may require amounts upwards of 1,000 IU (25 mcg) daily (8).

Current Research and Roles

In the last decade, findings indicate that vitamin D's function is more dynamic than previously understood. Studies have recently associated vitamin D deficiencies in children to a wide-range of health conditions including: allergies, asthma, dermatitis, insulin resistance, seizures, and behavioral disorders (16, 20, 24, 35, 37). Moreover, some studies have shown the potential of vitamin D supplementation as not only a preventative measure for these associated ailments but also a treatment (16, 37).

Vitamin D Receptor

Advances in molecular and cellular biology allow for study of vitamin D on the cellular level. Receptors for vitamin D have been discovered in over 50 tissues (17). Locations of vitamin D receptors (VDR) have been found in high expression in the intestines of the digestive system, beta islet cells of the pancreas, the nephrons of the kidneys, parathyroid gland of the endocrine system, bronchi of the respiratory system, thymus of the immune system, osteoblasts of the skeletal system, and within the brain (17). The role of vitamin D in calcium homeostasis involves several of the aforementioned systems of the body where receptors are of high density including the digestive, endocrine, renal, immune and skeletal systems. High density of VDR's in areas that are not known to regulate calcium homeostasis, merits attention as the exact role of vitamin D receptors in tissues of the body where other physiological processes occur has yet to be elucidated.

VDR in the Brain

The human brain is one site of VDRs of recent interest. The VDR and the enzyme to convert 25 hydroxyvitamin D to the active form 1,25-dihydroxyvitamin D, 1 α-hydroxylase, are present in the human brain (18). VDRs are found in areas of the brain involved in learning, cognitive functioning and memory (19). This has gained interest with many researchers for its role in neurodevelopment and possible neural-related consequences of deficiency in children. As a neurosteroid, vitamin D is known to regulate gene expression in the brain, contributing to cell differentiation in neurodevelopment (19). Researchers have recently looked at the potential link of vitamin D in psychiatric disorders finding that vitamin D through gene regulation controls a step in the production of serotonin (20). These findings are huge as many clinicians are concerned with the rise in neuropsychiatric disorders in children, many of which involve serotonin imbalances. Recent studies are also researching the role of vitamin D in relation to immune and metabolic disorders including allergies and insulin resistance.

Role in the Immune System

Although commonly known for its activity in calcium homeostasis, vitamin D also has a role in the immune system. Adequate vitamin D during childhood is especially important for the immune system since first encounters with pathogens occur during childhood. Early years of development dictate in part the course of future immune activity. Studies as early as the 1980's have shown that vitamin D has immunomodulatory properties. Vitamin D inhibits specific immune T cells which lie in the thymus (21). Interestingly, the thymus is larger in childhood and diminishes in size in adulthood. Studies found that the thymus has high expression of VDR (17). T cells of the thymus regulate the adaptive immune response, which deals with environmentally encountered pathogens. This aspect of the immune system is known as the adaptive immune system. When the adaptive immune system is mistakenly activated or deregulated, allergies such as allergic asthma, atopic dermatitis and food allergies can occur.

Allergic Disease

Recent findings of the last decade associate low levels of vitamin D with asthma and allergic disease. A study published in 2012 issue of International Archives of Allergy and Immunology found that compared to non-asthmatic children in Qatar, vitamin D deficiency was significantly higher in asthmatic children. The results showed that above 20 ng/ml, the cut-off for deficiency, asthma occurrence decreased as vitamin D serum levels increased (22). In a 2014 issue of the Journal of Pediatrics, a study on over 200 infants linked vitamin D levels to food allergies and atopic dermatitis. An inverse relationship was identified between vitamin D levels and atopic dermatitis, as well as an association between low levels of vitamin D and increased food allergen sensitization (23). Vitamin D insufficiency early on is believed to be a risk factor for food allergy (23, 24). Although current data is limited and inconsistent, these associations and trends may still be useful for the pediatric community as food allergies are often observable within the first year of life.

Pediatric Irritable Bowel Syndrome

Irritable Bowel Syndrome (IBS) explains chronic gastrointestinal tract issues including abdominal pain, flatulence, diarrhea, and constipation. Studies in adults with IBS have previously shown an improvement of symptoms with supplementation of vitamin D3 (25). A study published this year on vitamin D deficient children with IBS showed that vitamin D3 supplementation improved IBS symptoms significantly, compared to the control group (26). The results of this study do not provide a mechanism for how vitamin D3 may be acting however several potential explanations were discussed. The authors mention the role of vitamin D in the immune system and the inflammatory response. IBS sufferers have mucosal inflammation activated by immune cells that vitamin D is known to modulate (21,26). Further studies must be conducted to explain how vitamin D3 supplementation is helping alleviate symptoms of IBS. Currently, data does suggest a therapeutic role of vitamin D3 supplementation for children suffering from IBS.

Diabetes and Insulin Resistance

Among children today, the rates of obesity, diabetes mellitus and insulin resistance are alarming. A 2018 review assessing associations of insulin resistance, diabetes, and obesity with vitamin D status uncovered several connections. The review, published in The Journal of Steroid Biochemistry and Molecular Biology, examined over 200 articles. The findings indicate that a deficiency in vitamin D may impair insulin release based on the action of vitamin D binding to the VDR on beta-islet cells of the pancreas, signaling the release of insulin (27). Although some research was questioned on experimental design, overall the review concluded supplementation with vitamin D3 may help insulin sensitivity.

Data from a 2016 study on adults showed a significant improvement of insulin sensitivity with vitamin D3 administration within two months (28). The findings in the pediatric population also seem promising. In a 2018 study of over 2,000 school children in Greece, an association was found between insufficient vitamin D levels and insulin resistance that was independent of obesity (29). Low vitamin D levels have also been associated with insulin resistance in Brazilian children (30).

Although the aforementioned studies are promising, the research findings are not all in agreement. A systematic review from 2016 claimed inconclusive results for confirming a connection between vitamin D and insulin resistance (31). One study published in Diabetes may explain some downfalls of the narrowly designed investigations on vitamin D and glucose regulation that lead to conflicting findings. The study published in Diabetes suggests considering the entire parathyroid hormone (PTH) vitamin D axis when assessing possible involvement in glucose regulation (32). A major role of PTH is to stimulate conversion of vitamin D into its active form for mineral absorption. When vitamin D availability is sufficient, it completes a negative feedback loop on the parathyroid gland by suppressing the secretion of PTH. When someone is deficient in vitamin D, their PTH levels may be elevated do to the lack of vitamin D required to sufficiently suppress the parathyroid gland. Conducted on 494 postpartum women, this study showed that vitamin D deficiency in conjunction with high levels of PTH predicted decreased insulin sensitivity, pancreatic beta-cell dysfunction, and poorly regulated glucose homeostasis (32). The researchers determined that these health effects were not observed in women with insufficient vitamin D yet moderate regulation of PTH. Thus, it is possible that glucose regulation may be affected by the combination of low levels of vitamin D and subsequent elevated PTH levels. There is still much research to be done to fully understand the role of the PTH vitamin D axis on glucose regulation but at present there may be a benefit for pediatricians to consider assessing not only the vitamin D status of a child but their entire PTH vitamin D axis to ensure levels of vitamin D sufficient for PTH suppression are being met. As issues with glucose regulation are becoming more prominent in pediatric populations, the findings from research on diabetes-related health issues over the last decade has provided valuable information for clinicians to consider when assessing patients. These findings stress further the importance of vitamin D supplementation.

Autism

According to the Centers for Disease Control (CDC), autism is one of the fastest growing developmental disabilities. In a study by the CDC among U.S. children 8 years of age in 2002, about 1 in every 150 children was diagnosed with autism spectrum disorder. In 2014, the CDC found among children 8 years of age an estimated 1 in 59 was diagnosed with autism spectrum disorder (33). Studies have implicated a possible link between vitamin D deficiency and autism spectrum disorders. Clinical reviews have found that a deficiency in vitamin D may be a trigger in predisposed children for autism spectrum disorders (34). Observed correlative trends between latitude, autism and vitamin D deficiency were found. Autism rates are lowest near the equator, where there is the highest amount of solar radiation, a source for vitamin D synthesis, while highest rates are reported further away from the equator in regions where vitamin D production from skin exposure to sun is insufficient at providing adequate amounts of vitamin D (35). Although evidence is indirect, the trends offer a potential role for vitamin D in autism spectrum disorders and opportunities for further research.

Therapeutic Objective

Pediatricians should keep in mind the potential of vitamin D3 administration as a form of therapy. Not only does administration help in correcting a vitamin D deficiency, it has been implicated to improve conditions of several ailments (36, 37).

Although further research is necessary to identify the connection between autism and vitamin D deficiency, at this point there is evidence for a therapeutic use of vitamin D supplementation to aid in managing symptoms of autism. A 2012 study conducted on over 100 children with autism spectrum disorder showed that of the 83 subjects with clinical vitamin D deficiency who completed a three-month daily supplementation regime, over 80% showed a significant improvement in behaviors, eye contact, and attention span (36).

In a 2014 published study on epileptics with vitamin D deficiency, administration of high dose vitamin D3 (1,000-5,000 mcg depending on severity of deficiency) followed by 50-65 mcg supplementation for three months showed significant reduction in seizure occurrence, with a median reduction of 40% (37). Large scale studies should be conducted to corroborate the practice of vitamin D3 as therapy for children with seizures. Additional studies of different magnitude must be conducted to unravel the full potential of vitamin D3 on development, and prevention of ailments in children. At present, significant results in therapeutic effectiveness of vitamin D supplementation for several disorders in the pediatric population provide a foundation.

Optimal Vitamin D

The last decade has provided clinicians and the scientific community with a wealth of new knowledge on vitamin D in health. The preventative benefits of vitamin D as well as the therapeutic, supports a reconsideration of the amount of vitamin D that is actually optimal for wellness. Although it is agreed upon that the amount of vitamin D needed to sufficiently regulate calcium homeostasis and prevent rickets is at 20 ng/ml, the recent findings on novel roles of vitamin D in the body bring to question the optimal amounts of vitamin D for other aspects of child development.

There is much debate still over the amount of vitamin D deemed optimal. The Institute of Medicine (US) exerts cautionary measures when setting the tolerable upper limit for infants and children. The tolerable upper levels are set at 1,000 IU (25 mcg) for children 0-6 months of age, 1,500 IU (38mcg) 7-12 months, 2,500 IU (63 mcg) 1-3 years, 3,000 IU (75 mcg) 4-8 years and 4,000 IU (100 mcg) 9-18 years (9). These values are based on maintaining normal calcium levels and prevent rickets for the majority of people. The optimal amount to not only maintain calcium homeostasis but additionally enhance the extra-skeletal benefits of vitamin D could conceivably be higher. Studies in the last decade implicate benefits of disease prevention at serum levels above the 30 ng/ml recommended, up to 100 ng/ml (38).

A Short Communication in a 2012 issue of the *British Journal of Nutrition*, stated that among people in East Africa that follow a traditional lifestyle of hunting and gathering, the average serum vitamin D levels were 115 nmol/L (46 ng/ml). They also noted that Caucasian lifeguards in the U.S. had comparable levels above 100 nmol/L (40 ng/ml) (39). This suggests that the body does naturally produce an amount significantly greater than the minimum 50 nmol/L (20 ng/ml), and that it is biologically possible and perhaps optimal to live with levels more than double the recommended minimum.

Conclusion

New scientific findings from the last decade indicate that vitamin D may be a greater contributor to overall health. The benefits of vitamin D have been found to extend far beyond the basic health of the skeletal system. Vitamin D receptors have been found in major organs throughout the body, in areas researchers previously believed vitamin D had no function or need. Vitamin D deficiencies have been implicated in a wide-range of ailments that afflict children. Moreover, vitamin D administration has been beneficial as therapy for conditions such as seizures. With the increasing knowledge of the benefits of vitamin D, many organizations advocate for increased recommendations for daily intake. To achieve a holistic perspective, it is important to consider all the benefits of vitamin D, as well as the consequences a deficiency may have on a growing child. While it is not impossible to obtain adequate vitamin D through solar radiation and dietary intake alone as seen in African communities, significant evidence suggests that many children in Europe, Asia, and the U.S. do not obtain adequate amounts through sun exposure or diet. For this reason, the importance of obtaining adequate amounts through daily supplemental intake should be stressed.

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