VITAMIN D: A LITERATURE REVIEW ON ITS EFFECTS AND RELATION WITH THE USE OF SUNSCREEN PRODUCTS

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ABSTRACT

Vitamin D is crucial for homeostasis of calcium and phosphorus and for musculoskeletal and cardiovascular health and disease. Its deficiency may be related to several autoimmune diseases and some cancers. A major pathway of vitamin D synthesis occurs in skin, mediated by the sunlight, but it can also be obtained from the food or vitamin supplements. Ultraviolet B radiation is responsible for various effects on human health. Beneficial effects as the synthesis of vitamin D, but also detrimental ones, as the development of skin cancer. Concern about the risk of skin cancer led to the diffusion of large-scale photo protection. The purpose of this article is to make a detailed and updated review on vitamin D, its main sources, effects on the human organism and factors affecting its production. Problems associated with low vitamin D levels and the use of sunscreens are also discussed.

KEYWORDS: Vitamin D, ultraviolet B radiation, skin cancer, sunscreens.

1. INTRODUCTION

Vitamin D is a steroid hormone crucial for musculoskeletal and cardiovascular health as well as for the homeostasis of calcium and phosphorus. Its deficiency may be associated with some types of cancer and various diseases such as multiple sclerosis, diabetes mellitus types 1 and 2, systemic lupus erythematosus, inflammatory bowel disease, among other[1].

Lately, concern about the risk of skin cancer led to the diffusion of large-scale photoprotection and currently there are two divergent positions by physicians: on one hand the community of dermatologists and, more recently, the World Health Organization, guiding patients about the use of sunscreen to avoid any exposure to the sun. On the other hand are doctors who recommend the need for sun exposure to ensure a good level of vitamin D[2].

In a general way, vitamin D produced in the skin remains in the body up to two times more than vitamin D ingested in the diet. In addition, most humans must have only a few minutes of sun exposure daily to maintain healthy levels of vitamin D during the year[1]. However, the spectrum of UVB radiation required for the activation of vitamin D in the skin is a recognized carcinogen factor to keratinocytes[3].

Thus, this paper aims to review the literature on the importance of vitamin D for homeostasis and the consequences of the reduction of its synthesis by use of sunscreens.

2. MATERIAL AND METHODS

In the present study the guiding question of the integrative review was: contribute to technical information for professional health care.

Bases (Latin American and Caribbean Literature on Health Sciences) LILACS, SciELO (Scientific Electronic Library on Line) and PubMed (NCBI US National Library of Medicine National Center for Biotechnology Information) were consulted. Studies that have addressed the thematic, published from 1975 to 2014, regardless of the languages of publication were included.

3. LITERATURE REVIEW

Vitamin D consists in a group of lipophilic pre-hormones, which are converted in the body into several biologically active metabolites that function as hormones circulating in the blood and regulating the activities of several cell types[4].

This vitamin is a steroid wherein ring B of the nucleus of the molecule is replaced by non-saturated hydrocarbon bridge containing two double bonds. The cleavage of the C-C bond between C9 and C10 is essential to the change produced by the photochemical process [5].

The major source of vitamin D is the skin, stimulated by ultraviolet radiation; food sources contribute only with a small portion of the daily needs. Vitamin D3 or cholecalciferol is synthesized in human skin by the action of UVB radiation from 7-dehydrocholesterolas well as being found in foods such as fish oil and egg yolk[6]. Vitamin

D2 or ergocalciferol is formed from a fungal steroid ergosterol and are rarely supplied naturally in foodstuffs, but used as a food supplement[6].

Vitamins D2 and D3 differ in structure and metabolism, but their biological activities in humans are comparable. They are sterols with an open core, although they are thermostable, they are quickly degraded by light, oxygen and acid[5]. The chemical structures of vitamins D2 and D3 are shown in Figure 1.

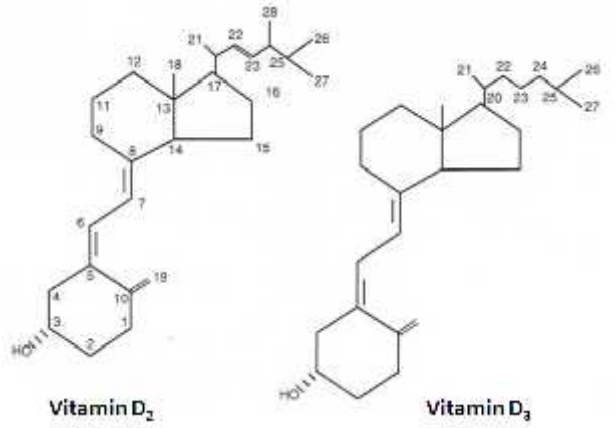

Figure 1. Chemical structure of vitamin D2 and D3. Aires [7]

One time ingested or synthesized in the skin, vitamin D is transported to the liver where it undergoes to first hydroxylation at carbon 25, converting to 25-hydroxy Vitamin D or 25(OH)VD. This is the main circulating form of VD, with a half-life of around two to three weeks[1]. In the kidney, 25(OH)VD undergoes a new hydroxylation with the production of the active form, 1,25-dihydroxy vitamin D or 1,25$(OH)_2$D. Although this is the active form, is not suitable to an estimate of the body´s stock of vitamin D, because it has a shorter half-life, around 6 to 8 hours[6].

In the blood, the transport of vitamin D is mainly made by vitamin D binding protein and to a lesser extent by albumin[8].

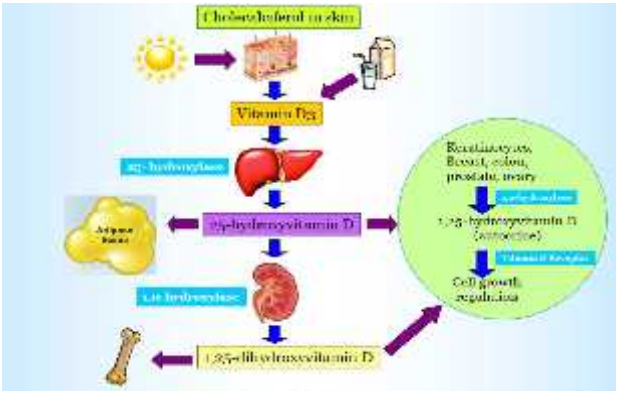

Figure 2. Synthesis of Vitamin D and effects on skeletal tissue and extra-skeletal tissues. Modified from Swati11[11]

Vitamin D exerts its biological functions through its binding to nuclear receptors, vitamin D receptors (VDR), which regulate the transcription of DNA into messenger RNA, similar to receptors for steroids, thyroid hormones and retinoids[9]. There receptors to vitamin D, virtually, in all tissues, such as brain, pancreatic islets, bone, skeletal muscle, kidney, intestine, skin, parathyroid, pituitary, breast, lymphocytes and monocytes[10].

2. Sources of Vitamin D

In humans, 90% of vitamin D comes from the skin by the sun-mediated synthesis. The remainder can be obtained from foods that contain vitamin D naturally in foods that have been fortified and the use of pharmaceutical products[12].

Natural sources are cod liver oil, tuna, salmon, egg yolks, swiss cheese, liver and sardines. Fortified foods include milk, juices, margarines, yoghurts and cereals. In pharmaceutical forms there are the vitamin D2 and D3 [12].

3. Effect of Vitamin D

Vitamin D exerts various effects on homeostasis, which are summarized below[2].

In bone, vitamin D prevents osteopenia, osteoporosis, osteomalacia, rickets and fractures. Vitamin D is required for maintenance of plasma calcium by increasing calcium absorption from the small intestine, mobilizing calcium from bone and reducing its renal clearance. Vitamin D plays important roles in the absorption and bone deposition. Low calcium absorption generates a number of physiological problems, since calcium is important for most metabolic functions, as well as the muscular activity[13,10]

In relation to cells, it has been shown that vitamin D may prevent certain types of cancer, such as prostate, pancreatic, breast, ovarian and colon cancer. Also prevents infectious diseases and infections of the upper airways, asthma and other respiratory illnesses. These effects occur because the genes regulated by vitamin D influence biological processes such as inhibition of cell proliferation, apoptosis and stimulate the production of bactericidal proteins[14].

Considering the immune system, adequate levels of Vitamin D appear to prevent multiple sclerosis, type 1 diabetes, Crohn's disease and rheumatoid arthritis. This occurs because the effect on the immune system of vitamin D translates into increased innate immune regulation associated with an acquired immunity. Vitamin D interacts with the immune system through its action on the regulation and differentiation of cells such as lymphocytes, macrophages and Natural Killer cell, besides interfering in production of cytokines[8, 9].

3.1 Other effects of vitamin D recently described

Recently, many studies indexed in PubMed related to

vitamin D. Below are some conclusions of the various medical specialties.

3.1.1. Obstetrics and Gynecology

Low maternal vitamin D levels during pregnancy may be associated with a higher risk of pre-eclampsia, gestational diabetes, preterm birth or small for gestational age neonates[15]. In addition, a study demonstrated that supplementation of pregnant women with 50,000 IU of vitamin D every two weeks significantly improved the insulin resistance during pregnancy[16]. The data from randomized controlled studies indicated that 4,000 IU / day of vitamin D3 during pregnancy "normalize" the metabolism of vitamin D and improve birth outcomes, including the rate of primary cesarean delivery and comorbidities, without risk of side effects[17]. It has been further shown that low levels of vitamin D increase the risk of rickets in the offspring, which leads to the need for all women to be informed, at the time of the query, the importance of adequate vitamin D stores during pregnancy and breastfeeding[18]. Still, it is described that obese women transfer less 25(OH)D to the fetus than women of normal weight, even with similar serum levels[19].

A vitamin D deficiency may be more common in premenopausal women than previously thought, and may compromise the quality of life by increasing weakness, fatigue, and nonspecific pain[20].

Furthermore, treatment with vitamin D3 had beneficial effects on some risk factors of cardiovascular disease by reducing serum levels of total cholesterol, triglycerides and VLDL in patients with polycystic ovary syndrome and vitamin D deficiency[21].

3.1.2. Endocrinology

According to the work done in the Department of Exercise Nutrition and Physiology of the University of Missouri (USA), obese adolescents have a higher risk of vitamin D deficiency, because it is considered that vitamin D is sequestered by excess fatty tissue[22]. A BMI (body mass index) higher than the normal leads to lower levels of 25(OH)D, while possible effects of lower levels of 25(OH)D in the increase of the BMI are probably small[23].

Low levels of vitamin D were associated with a higher prevalence of metabolic syndrome, type 2 diabetes or both conditions in adults and adolescents[22].

It was described that replacement of vitamin D in mild primary hyperparathyroidism is safe, effective and does not increase calcium levels to dangerous levels[24].

3.1.3. Orthopedics

Hypovitaminosis D is common among children with fractures of the upper extremities[25]. A level of 25(OH)VD of 65 nmol/L is required to reduce the risk of non-vertebral fractures and 75 nmol/L may be necessary to reduce the risk of hip fractures[26]. Most patients of both genres, aged 18 or more and featuring hip fractures showed vitamin D insufficiency, and those with 71 years or older had significantly lower levels of 25(OH)D when compared to a control group submitted to total arthroplasty[27].

3.1.4. Pediatrics

Maternal vitamin D insufficiency during lactation, related to the lack of sun exposure and a minimal intake of vitamin D in the diet contributes to low vitamin D in breast milk and therefore to vitamin D deficiency in the baby[28]. As for school-age children, studies suggest that vitamin D deficiency is associated with an increased incidence of gastrointestinal infections and otitis[29].

3.1.5. Dermatology

The vitamin D levels in children are correlated with severity of atopic dermatitis, but only in patients with allergic sensitizations. It is believed that vitamin D affects the progression and severity of atopic dermatitis[30].

3.1.6. Cardiology

The deficiency of vitamin D has a positive correlation with blood pressure and hypertension may be related to the non-dipper type (without a nocturnal decrease). The measurement of vitamin D may be used to indicate a higher risk of adverse cardiovascular events related to hypertension[31]. Other clinical studies support the concept that vitamin D deficiency is involved in the pathogenesis of cardiovascular and renal disease through its association with diabetes, obesity and hypertension. This fact is particularly important for African Americans and women in postmenopause, that present an additional risk of cardiovascular disease. It is suggested that the adverse cardiovascular effects of low levels of vitamin D in postmenopausal women could be reduced by a combined therapy of vitamin D and sex steroids which act via endothelial dependent or independent mechanisms, resulting in the generation of nitric oxide and calcitonin gene related peptide[32].

It has been reported that vitamin D deficiency may influence the increase in blood pressure because the vitamin suppresses the biosynthesis of renin, which activates the renin-angiotensin-aldosterone, [14].

3.1.7. Central nervous system

The deficiency of vitamin D has been associated with a higher risk of depression and schizophrenia. Vitamin D affects the brain regardless of the hormonal pathways that regulate serum calcium. The non-significant difference in the serum level of vitamin D among schizophrenic and depressed patients suggests that the effect into the brain is a generalized one and not restricted to a specific region or via in the brain[33].

Finally, with respect to the central nervous system, vitamin D appears to prevent Alzheimer's disease and dementia. This occurs by immunomodulation, regulation of neuronal calcium, antioxidant mechanisms, increased neuronal conduction and detoxification mechanisms. As for the humor, it seems to prevent seasonal affective disorder, premenstrual syndrome and disorders of sleep, increasing the feeling of well being[2, 14].

4. Identification of body levels of vitamin D

The most reliable test for evaluating the level of vitamin D is the measurement of 25-hydroxy Vitamin D or 25(OH)VD in the serum. 25(OH)VD has a serum half-life of 2 to 3 weeks, and its measurement in serum is considered to be the ideal marker of vitamin D stores in the body[10].

The $1,25(OH)_2VD$, despite being the active form, is normally not measured, since the half life is short (about 6 hours). Furthermore, in the case of vitamin D deficiency, there is a compensatory increase in the secretion of parathyroid hormone (PTH), which stimulates the kidney to produce more $1,25(OH)_2VD$. Thus, when vitamin D deficiency occurs and there are a decrease in levels of 25(OH)VD, concentrations of $1,25(OH)_2VD$ remain within normal levels, and in some cases even higher levels are found[8].

The main vitamin D toxicity is hypercalcemia. Unlike vitamin D supplements, neither exposure to the sun nor artificial tanning cause intoxication, which is linked to several serious symptoms, including nausea, vomiting, loss of appetite, constipation, increased thirst, increased urination, depression, calcification of the kidneys and renal failure[2,5].

Table 1. Recommended intake of vitamin D, according to the different age groups.

Age	Estimated average needs (IU/day)	Daily dose Recommended (IU/day)	High dosage (IU/day)
0-6 months	0	0	1000
6-12 months	0	0	1500
1-3 years	400	600	2500
4-8 years	400	600	3000
9-70 years	400	600	4000
>71 years	400	800	4000
14-18 (pregnant and lactating)	400	600	4000
19-50 (pregnant and lactating)	400	600	4000

Source: Modified data from the Institute of Medicine (IOM) of the National Academy of Sciences of the United States, 2014 (in www.iom.edu).

Currently most authors adopt the following values for the levels of vitamin D in the human body: A) deficiency (<20 mg/ml), B) failure (21-29 mg/ml), C) normal reference range (30-100 mg/ml), D) Poisoning (> 150 mg/ml)[2]. The daily intake of VD recommended by the Institute of Medicine of the National Academy of Sciences of the United States, in different age groups is shown in Table 1.

5. Factors which affect the Vitamin D' production

There are endogenous and exogenous factors that affect the production of vitamin D[14]. These factors are described below.

5.1 Endogenous factors

5.1.1 Pigmentation

Black and white people have the same ability to produce vitamin D. The difference lies in the amount of melanin, because melanin is a natural sunscreen. Studies show that the epidermal conversion of 7-dehydrocholesterol to pre-vitamin D in the skin phototype II (fair-skinned Caucasians) is 5-10 times more efficient than a phototype V (Hindu or Asian with dark brown) skin. Dark-skinned individuals synthesize less VD when exposed to the same amount of radiation[14].

5.1.2. Age

The physiological changes associated with aging are related to low levels of vitamin D in the elderly because there is reduced capacity to generate its precursor in the skin, 7-dehydrocholesterol which turns into vitamin D3 by the action of UVB rays. Such effects arise by daily use of sunscreen, change of lifestyle and reduced physical activity outdoors. The vitamin D production is affected as the skin thins with age[1].

Regarding young people, the childhood and adolescence are considered critical periods of vulnerability to the effects of sun exposure. The skin photoaging is started early in childhood with inadequate sunlight exposure. Besides, excessive sun exposure in this age group is a particularly significant factor in the future risk of developing skin cancer. About 25% of sun exposure of an individual's life occurs before 18 years of age[34].

Moreover, in the elderly the probability of death due to fractures (especially hip) caused by osteoporosis and other causes related to vitamin D deficiency is much higher than death from skin cancer[1, 2].

5.1.3. Body mass index:

Patients with higher body weight have lower vitamin D levels than people with normal weight. This is because the vitamin D excess accumulates in the fat, so that it cannot be properly used in the absorption and deposition in bone[1].

5.1.4. Liver and kidney diseases

The kidneys and liver are two key organs for the production of vitamin D. All patients with kidney or liver disease will likely have problems with the production of VD and therefore should receive vitamin D supplements[2].

5.1.5. Drugs which interfere in metabolism of VD

Some drugs like antifungals, anticonvulsants, antiretrovirals, corticosteroids and St. John herb, among others increase the destruction of vitamin D in the body [2].

5.2. Exogenous factors

5.2.1. Altitude above sea level

Ultraviolet radiation is more intense at higher altitudes because there is a smaller amount of air for its absorption. In the higher altitudes the probability of overexposure is greater [1].

5.2.2. Latitude

The solar radiation is more intense at the equator, where the sun shines directly and the route of its radiation through the ozone layer is the lowest of all. At the equator, a larger volume of ultraviolet radiation reaches the soil surface[1, 2].

5.2.3. Pollution

Pollution can filter out UV radiation and, therefore, a smaller volume of UV reaches the ground[2].

5.2.4. Season

The angle of the sun changes according to the seasons of the year. This causes variation in the intensity of ultraviolet radiation, which is greater during the summer months[1].

5.2.5. Clothing

People that use clothing from head to toe, for example, in some cultures, may have vitamin D deficiency by not exposing the body to the sun[1].

5.2.6. Sunscreen usage

Sun exposure produces some adverse health effects. The use of sunscreen prevents almost completely, the production of vitamin D in the body, as it blocks UVB radiation [10].

6. Reactivity to sunlight and skin types

In dermatology, the best classification for the types of skin is proposed by Fitzpatrick[35] that classifies the individual according to your skin type[34]. This classification is shown in Table 2.

Table 2. Types of skin reactivity in relation to the sun.

Type	Skin color	Performance of the skin to the sun
I	Very fair skin Caucasians	They burn easily and never tan.
II	Fair-skinned Caucasians	They burn easily and tan slowly and with difficulty.
III	Caucasian skin lightly brunette	They rarely burn and tan relatively easy (light brown).
IV	Caucasians slightly dark skin	They virtually never burn out or tan readily with little burn (moderate brown color). Some individuals with Mediterranean origin or ancestry.
V	Asian or Hindu	Rarely burn and deeeply tan (dark Brown color)
VI	African Caribbean or Black people	They never burn and are intensely pigmented.

Source: Modified from Criado[34]

7. Photoprotection X Vitamin D

The sun is the main source of heat and ultraviolet radiation to the earth, and is the major source of vitamin D in human [36]. Ultraviolet radiation is non-ionizing electromagnetic wave composed of three ranges: UVC (100 to 280 nm), UVB (280 at 320 nm) and UVA (320 to 400 nm)[36]. In general, the UV does not reach the ground and UVA radiation penetrates deeper into the skin than UVB radiation[36].

Ultraviolet radiation from the sun that reaches the earth's surface is made up of 95% UVA and 5% by UVB[36]. UVB radiation is the ultraviolet spectrum responsible for cleaving the provitamin D (7-dehydrocholesterol) to pre-vitamin D in the skin. On the other hand, it is also the most biologically active factor in skin carcinogenesis[36].

The skin has two layers, the outer, called epidermis and the inner called the dermis. The dermis contains blood vessels, lymph ducts, fibers, nerve endings and hair follicles. The epidermis is thinner than the dermis and is made of squamous cells (keratinocytes). Under these squamous cells, there are cells with more rounded shape, termed basal cell. The basal cells constantly divide to rejuvenate the skin. They are positioned at the top of the epidermis, where they are programmed to die and form the outer layer of dead skin (stratum corneum). The stratum corneum acts as a mirror that reflects both UVA and UVB radiation from the sun, away from the skin. Interspersed in the basal cells are melanocytes. The melanocytes produce melanin that protects the skin cells against sunburn, because they absorb ultraviolet radiation[2].

There is a dose-dependent relationship between solar exposure (cumulative) and the development of cutaneous carcinomas - squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), jointly referred to as non-melanoma skin cancer (NMSC) - and also a marked relationship between intermittent sunburn and the development of malignant melanoma (MM)[34].

The NMSC is the most common skin cancer and accounts for 25% of all malignant tumors registered in Brazil. From these, basal cell carcinoma accounts for 70% of diagnoses. It shows high cure rates if detected

early. It is more common in people over 40 years and it is relatively rare in children and blacks, except those already suffering from previous skin diseases. The main victims are people with light skin, sensitive to the action of sunlight or previous skin diseases [37].

The MM is less common and accounts for 4% of malignant tumors registered in Brazil. It is a type of skin cancer that originates in melanocytes, has predominance in white adults and is more severe due to high possibility of metastasis[37].

According to INCA and the Ministry of Health (2014), estimates are that the non-melanoma skin cancer is the most frequent, with a forecast of 182 000 new cases[37].

The risk of skin cancer have led dermatologists to prescribe sunscreens to the population, indicating to them to avoid exposure to the sun and replenish the sunscreen whenever necessary[3]. The existing sunscreens are products that have in their composition, substances called solar filters. These, in turn can be divided into organic and inorganic ones. Organic chemical filters absorb UV radiation, reducing its effect on the human body. Inorganic physical filters offer protection by reflection of the incident radiation[3]. When the sunscreen is topically applied properly (2 mg/cm^2), there is a reduction of approximately 95% in the production of vitamin D_3[1].

Sun exposure produces adverse effects on the health of the skin and is the main trigger factor for skin cancer and for this reason there are campaigns that recommend avoiding sun exposure and encourage the use of sunscreens. However, currently this position is controversial, since the same ultraviolet rays that are necessary for the production of vitamin D, with all its benefits, are blocked by the use of sunscreens[3].

Moreover, it is estimated that in terms of time of sun exposure, approximately 20% of the body surface (arms and/ or legs), for 5 to 15 minutes between 10 and 15 hours 2 to 3 times per week for summer, spring and autumn is a sufficient amount of sun exposure to increase levels of vitamin D. After this time one should use sunscreen with a protection factor appropriate to the skin type[1].

4. CONCLUSION

Vitamin D is very important for the health of the human being, and maintaining adequate levels of vitamin D not only brings benefits as it prevents a number of diseases. However, the data are contradictory and there is no consensus within the medical society both with respect to the existence of a sufficient and safe level of sun exposure in order to maintain an optimal level of vitamin D, as well as what would be the amount of vitamin D that should be administered in patients with deficiency/ insufficiency. There are uncertainties also concerning its usage for specific pathological conditions, time of treatment and the maintenance dose.

Anyway, one should avoid radical guidelines, such as avoiding the sun at any time and continuously use sunscreen during the day in all age groups, because there is no general rule. The physician should be alert, before prescribing the best treatment, to some issues such as the disease the patient presents. There are some groups of people to which sun exposure is contraindicated as transplant patients, individuals with lupus, those with a predisposition to develop cancer skin, or in use of immunosuppressive drugs, among others. There are other groups of patients who have risk factors for vitamin D deficiency, but that can sunbathe, such as patients with lactose intolerance, intestinal malabsorption, renal failure, cystic fibrosis, liver disease. Also, there is another group of people who use some medications that decrease the level of vitamin D as antifungal drugs, anticonvulsants, antiretrovirals, and glucocorticoids. Thus, the best treatment should be the one in which the doctor examines the patient and all his medical history and, based on the risk-benefit, prescribes what is most appropriate for the patient in that circumstance.

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