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Review

Vitamin D – The True and the False about Vitamin D

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A B S T R A C T

Vitamin D has a positive impact on our overall health. Also there are a few conditions with strong evidence for a protective effect of vitamin D, such as bone diseases, internal cancers, multiple sclerosis, hypertension and DM type 1. Skin is the major source of vitamin D through the action of UVB light on keratinocytes, although the biologically active form of vitamin D is not exclusively produced in the kidney, but also in prostate, colon, skin and osteoblast where it acts as an autocrine or paracrine hormone. In the past decade raising incidence of skin cancers, especially melanoma and its connection with sun exposure lead to a sun protection policies and practices as part of the public health campaigns. The question is how much solar UV exposure is adequate to maintain the balance between the risk and the benefit. We as dermatologists have to raise public awareness of the potential health effects from excessive exposure to UV radiation but also we have to be aware that adequate blood level of vitamin D is necessary for optimal health. So future recommendation on sun protection have to balance between the risk and benefits of sun exposure, as well as to promote vitamin D supplementation as a safe alternatives in high risk population.

Key words: *vitamin D, UVB, sun protection policies, vitamin D supplementation*

History of Vitamin D

Vitamin D has been discovered 80 years ago, but first evidence of vitamin D deficiency occurred during the seventeenth century in the northern Europe with the industrial revolution. In the crowded, big cities polluted by the pall due to the burning of coal children by the age of 2 developed severe growth retardation and deformities of the skeleton that persisted throughout the afflicted life[1]. In 1822 Sniadecki recognized the association between the lack of sunlight in the Warsaw and the rickets, but it was not until 1919 that Huldschinsky reported successful cure of rickets within 3 months after exposure to ultraviolet radiation from a mercury arc lamp. The connection between the exposure to sunlight or artificial UV radiation and the cure of the rickets led to the concept of irradiating various foods. Steenbock first recommended irradiation of milk fortified with provitamin D. Vitamin D fortification in 1930s eradicated rickets as a significant health problem. Today in United States milk, some cereals and bread are still fortified while in Europe milk is not fortified but instead are margarine, some cereals and bread.

Biology of Vitamin D

Vitamin D is fat soluble vitamin that exists in two forms, as cholecalciferol (vitamin D_3) and ergosterol (vitamin D_2). Vitamin D_3 is naturally occurring form from animal food, while vitamin D_2 is produced in plants, primarily yeast when exposed to ultraviolet B radiation (UV-B). The main source of vitamin D is the endogenous production of vitamin D_3 in human skin through the action of ultraviolet B (UV-B) radiation. Normally 90% of the body's needs in vitamin D has to be produced in the skin because with the exception of some kind of fatty fishes (herring, salmon, mackerel, sardine, etc.) other foods contains only limited amounts of vitamin D[2]. The photosynthesis of vitamin D_3 occur in the basal and suprabasal layers of the skin$_3$ transforming the 7-dehidrocholesterol (provitamin D_3) in previtamin D3 which is then isomerised to vitamin D_3. Vitamin D_3 is inactive form and needs to be activated through the hydroxylation first in the liver at the C25 position, generating 25-hydroxyvitamin D_3 (calcidiol, or 25(OH) D_3). The second hydroxylation occur in kidney at the C1 position producing the active form, calcitriol (1α, 25-dihydroxyvitamin

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D_3, or 1α, $25(OH)_2D_3$). The hydroxylation in the kidney is stimulated by parathyroid hormone (PTH) and suppressed by phosphate. The production of 1α, $25(OH)_2D_3$ is under tight feedback control, directly by serum calcium and phosphate and indirectly by calcium through the decrease of PTH. In the circulation all forms of vitamin D are biding to carrier proteins, mostly vitamin D-binding protein (DBP) and albumin.

There are some evidence that keratinocytes also express a 1α-hydroxylase, and thus they are able to produce substantial amount of $1\alpha,25(OH)_2D_3$[4]. The cutaneous production of calcitriol have an intracrine et autocrine effects on keratinocytes and paracrine effects on surrounding cells promoting cellular differentiation and apoptosis[4]. Some new investigations have shown that skin fibroblast also express the 25-hydroxylase thus producing $25OHD_3$. Lacking the expression of 1α-hydroxylase, fibroblasts can not produce calcitriol but they may play an important role in the supply of precursors ($25OHD_3$) for keratinocytes and circulating blood[5].

Molecular mechanism of vitamin D

Vitamin D is a lipophilic molecule that easily passes cellular membranes and binds to the nuclear VD receptor (VDR). VDR is a member of a nuclear receptors super family that consist of eight different receptors for steroid hormones, receptor for vitamin D (VDR), receptors for thyroid hormone and receptors for vitamin A-derivate all-*trans* retinoic acid (T_3R and RAR). Most of the action of vitamin D is through the activation of VDR receptor in nucleus making the complex heterodimer with the retinoid receptor leading to the transcription ant translation of the genes forming various proteins – this is called »genomic« action of vitamin D. The »nongenomic« action is probably mediated through binding of vitamin D to the membrane receptors initiating the cascade of reactions which result in intracellular formation of second messengers or phosphorylation of intercellular proteins – activating an intracellular enzyme or ion channel.

Classical Function of Vitamin D

The main function of vitamin D is to maintain serum calcium levels in the normal range by increasing calcium and phosphate absorption for the mineralisation of the skeleton. In children vitamin D deficiency and consecutive deficiency of calcium lead to impaired calcification of the cartilage causing rickets. In adults the same scenario lead to osteomalacia6 because newly formed bone matrix (osteoid) is not well mineralised. Deficiency of vitamin D also causes higher secretion of parathyroid hormone (PTH) due to the low serum $1\alpha,25(OH)_2D_3$ and low serum calcium resulting in high bone turnover and bone resorption causing bone loss and contributing to osteoporosis. Osteomalacia and osteoporosis increase the risk of bone fracture especially hip fractures[6].

Non-Classical Function of Vitamin D

Besides the classical target cells of Vitamin D such as intestine, bone and kidney vitamin D receptor has been demonstrated in most other tissues (hearth, skin, skeletal muscle, prostate, uterus, melanocytes, colon, liver,...)[7,8]. Also skin, prostate, colon, breast and many other tissues express the enzyme to convert 25(OH)D to the active form $1,25(OH)_2$ vitamin D regulating cell growth[9]. Skin keratinocytes are the only cells in the body with the whole pathway from 7-DHC to $1\alpha,25(OH)_2D_3$, so they are both the site of calcitriol synthesis and target of this hormone. The active hormone regulates proliferation (inhibiting proliferation in high doses, stimulating proliferation in low doses)[10], differentiation and apoptosis of keratinocytes and other cells. The positive action of vitamin D analogues to skin diseases with impaired proliferation is due to its antiproliferative and prodiferrentiating effects.

There is some evidence in the recent past that vitamin D metabolites may protect against diabetes mellitus type 1 down regulating dendritic and Th 1 cells, promotion of Th2 lymphocytes, suppressing the antigen-presenting capacity of macrophages[11]. Several ecological studies have shown a relationship between lower sunshine exposure, higher latitude and vitamin D synthesis in skin with the higher cancer prevalence or mortality for colon, breast and prostate cancer[12,13] as well as for malignant lymphomas[14]. Deficiency of vitamin D plays a role in the pathogenesis of some auto-immune disease. Lower risk of multiple sclerosis is associated with the higher sun exposure in the puberty[15].

Factors that Influence Vitamin D Synthesis

Sun exposure

Sunlight is by far the best source of vitamin D for most humans; therefore any limitation in sun exposure may lead to vitamin D deficiency. The production of vitamin D is dependent on UVB radiation which has great seasonal and daily variations. The UVB insulation is maximal around noon in the summer. During winter at northern latitudes, the sunlight must pass longer distance trough the atmosphere absorbing the great proportion of UVB light. UVB is also effectively absorbed by glass and plastic[16]. Clothing and regular sunscreen use prevent the photosynthesis of vitamin D. In darker skin the capacity to produce the vitamin D is same as in light skin but due to melanin absorption longer exposure of UV-B is needed[17].

Age

Vitamin D production capacity is diminished with age due to a combination of skin getting thinner and a reduction in the concentration of vitamin D precursor 7-dehidrocholesterol. It has been estimated that above the age of 70, capacity to produce vitamin D is reduced to one-third that of 20-years old[1]. Elderly people also tend to spend most of the day inside; they protect their skin

from the sun by wearing long sleeves and using regularly sunscreens. Some investigators have found that intestinal absorption of vitamin D is reduced by 40% in the elderly, whereas others have reported no reduction[5].

Malabsorption results in malabsorption of fat soluble vitamin D, but also in calcium leading to secondary hyperparathyroidism and finally to increased 1,25(OH) $2D_3$ synthesis[18]. According to that the high risk population of developing vitamin D3 deficiency are elderly people, especially nursing-home residents, people with dark skin living in the higher latitude, those who have darker skin but cover most of the skin for religious reasons. Patients with skin type I, those who are under immunosuppressive therapy or have specific skin diseases (melanoma, Xeroderma pigmentosum) must be protected from sun exposure.

Vitamin D Deficiency

Severe vitamin D deficiency is accompanied by number of nonspecific muscular and skeletal symptoms such as bone and muscle pain, muscle weakness and cramps in extremities, fatigue and paresthesia[5]. The most important differential diagnoses are rheumatic diseases, polymyalgia rheumatica, and malignant disease. The problem is to determine what does vitamin D insufficiency mean and still there is no consensus on the borderline between vitamin D-deficient and vitamin D-sufficient state. Nutritional status of vitamin D is measured by the serum levels of $25(OH)D_3$ but the point is to determine whether we should define vitamin D deficiency based on population-based references limits for serum $25(OH)D_3$, health-based limits for PTH levels, hypocalcaemia or elevated alkaline phosphatase[6] or as the deficiency at the tissue level (bone and/or muscle diseases)[5]. Some authors propose cut off at 20 ngl/mL of serum $25(OH)D_3$ to define vitamin D deficiency[6,19], concentration that have protection effects from secondary hyperparathyroidism but is still consider by many authors to be too low. Published lower reference values are in range of 40–50 nmol/L. More recently according to defining vitamin D deficiency based on data from various biomarkers (PTH, calcium absorption) levels that are less of 32 ng/mL or 80 nmol/L are considered as deficient[20]. It may be concluded that is very difficult to delineate sharp diagnostic criteria for vitamin D deficiency or insufficiency and that we need careful studies to define optimal $25(OH)D_3$ concentration but it will certainly be higher than was previously thought.

How much vitamin D do we really need?

The other issues is to determine how much vitamin D must be ingested to reach the sufficient level of vitamin D to protect us against cancer and other diseases in cases when skin is not adequately exposed to UV radiation (winter time at high latitude, elderly in-patients, people with dark skin living in northern countries). The Recommended Dietary Allowance (RDA) of vitamin D is determined as daily dietary intake sufficient to meet the requirement of 98% of the individuals. The U.S. RDA from 1989 was 200 international units (IU)[21], but recently adequate intake in U.S. was defined to be 200 IU in adults until age 50 yr, 400 IU in adults from 51 to 70 yr, and 600 IU in the elderly over 70 yr. In Europe the RDA for vitamin D for adults from 18–64 yr as 0 to 400 IU and for elderly 65 yr and older is 400 IU[22]. The recent recommendation for paediatrics population issued 2008 from American Academy of Paediatrician (AAP) is 400 IU for breast feeding newborns until the consumption of 1000 ml of fortified milk daily.

Conclusion

It is well known that UV radiation provokes not only bio positive effects (*e.g.* production of vitamin D) but also bionegativ effects (*e.g.* skin aging and photocarcinogenesis). It is then essential to determine – how much UV light do we need to achieve sufficient vitamin D level, so we can take advantage of the beneficial effect of sunlight while preventing the damaging consequences due to excessive exposure to sunlight. Exposure of the body to one minimal erythemal dose (MED) of sunlight is equivalent to ingesting about 10 000 IU of vitamin D_3[21] therefore exposure of less than 18% of the body surface (hands, arms and face) to a 25%–50% of one MED in the spring, summer and autumn 2 to 3 times a week is adequate to satisfy body requirement of vitamin D. We as health care professionals have to recognised people at risk of developing vitamin D deficiency and monitor their vitamin D status. Vitamin D deficiency has to be prevented and treated by giving vitamin D orally[21,23] in recommended doses. Another option for treating vitamin D deficiency is administration of a single dose of 50,000 IU vitamin D once a week for 8 weeks or 50,000 IU once a month[21,23]. We as dermatologists have to raise public awareness of the potential health effects from excessive exposure to UV radiation but also we have to be aware that adequate blood level of vitamin D is necessary for optimal health. There is no doubt that excessive sun exposure is mutagenic and has to be avoided but very short and limited solar exposure is at certain times of the year sufficient for normal vitamin D synthesis. If anyone intending to stay at the sun more then optimal duration for vitamin D synthesis (it depends on latitude, season, skin type) use of sunscreen with minimal sun protection factor (SPF) 15 as well as wearing of protective clothes and sunglasses are essential. During the winter in most of the northern countries and in risk population vitamin D supplementation is a good substitution for low sun exposure and has to be recommended. In the future we need further work to determine influence of low sun exposure and vitamin D deficiency on occurrence of various cancers and health problems, including malignant melanoma[24].

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VITAMIN D – ISTINA I ZABLUDE

SAŽETAK

Dobro je poznato da vitamin D ima pozitivan utjecaj na cjelokupno zdravlje čovjeka, ali noviji dokazi govore ne samo o protektivnom utjecaju vitamina D na bolesti kostiju nego i za različite karcinome (dojke, debelog crijeva, prostate), multiplu sklerozu, hipertenziju i dijabetes tip 1. Osnovni izvor vitamina D za čovjeka je produkcija vitamina D3 u keratinocitima pod utjecajem UVB zraka, ali novija istraživanja upućuju da se aktivna forma vitamina D3 ne sintetizira samo u stanicama bubrega već i u keratinocitima, stanicama prostate, debelog crijeva, dojke gdje ima autokrini učinak na navedene stanice te parakrini na okolne stanice. Zadnjih godina povećana incidencija karcinoma kože posebno melanoma i dokazanog utjecaja UV zraka u patogenezi istih, uvjetovala je sve snažnije javnozdravstvene kampanje o zaštiti od sunca. Pitanje je koliku količinu UV zračenja trebamo da bi održali razinu između negativnog i pozitivnog djelovanja UV zračenja. Mi kao dermatolozi moramo sudjelovati u edukativnim i javnozdravstvenim kampanjama za zaštitu od pretjeranog izlaganja suncu, ali moramo biti svjesni da je adekvatna količina vitamin D neophodna za optimalno zdravlje. Kao preporuka u budućnosti sve javnozdrastvene kampanje moraju uzeti u obzir ne samo štetno djelovanje UV zraka već i njegov pozitivan efekt, kao i promovirati oralnu nadoknadu vitamina D posebno u zimskim mjesecima i kod rizične populacije.