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Vitamin D and innate immunity

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ABSTRACT: Vitamin D's role in bone health has been well established. Recently, studies have identified additional roles of vitamin D in the immune system, cardiovascular system, and cancer prevention. The effect of vitamin D on the immune system is particularly relevant to the dermatologist in that it has implications for atopic dermatitis, psoriasis, and skin cancer. However, there is much disagreement on a dose of vitamin D that is both safe and effective as both ultraviolet exposure and certain vitamin D-rich foods come with unwanted consequences. This review aims to update the dermatologist on the roles of vitamin D in the immune system, the safety and dose of different sources, and risk factors for vitamin D deficiency that may necessitate supplementation. Immune consequences of vitamin D status represent one additional aspect that illustrates how guidelines for supplementation are needed and will only be useful clinically if they are presented in context with validated controlled clinical trials.

KEYWORDS: immunity, supplement, UV exposure, vitamin D

Introduction

Vitamin D is best known for its role in calcium absorption and maintenance of healthy bones. However, numerous recent studies reveal that vitamin D has additional roles in the immune system, cardiovascular system, and cancer prevention. Vitamin D's role in the immune system has implications for atopic dermatitis (AD), psoriasis, and skin cancer. As evidence continues to clarify vitamin D's role in the immune system, it also highlights the role and possible benefit of vitamin D in each of these disease entities. This review will focus on the roles of vitamin D as it relates to the immune system and address areas of relevance for the dermatologist such as AD, psoriasis, and skin cancer. The review will also address the safety and dose of different vitamin D sources and risk factors for vitamin D deficiency that may necessitate supplementation. Although it will become clear that more evidence is needed to elucidate the full impact of vitamin D on the immune system and dermatologic pathology, exciting preliminary studies strongly support vitamin D's effect on immune defense.

At the forefront of any discussion on the immunological effects of vitamin D is an appreciation of the variables associated with intake, as well as the risks that can result from trying to extrapolate findings under one set of conditions to general conclusions regarding the physiological consequences of vitamin D. Although the benefit of vitamin D in bone health is generally accepted, it is the quantity, source, and relative physiological responsibilities of vitamin D that are central to the current debate. Unlike other vitamins that require dietary intake, the discussion of vitamin D is complicated by the well-known capacity of vitamin D3 to be generated by exposure of skin to ultraviolet B (UVB; 280–320 nm). Unfortunately, such exposure has the unwanted effect of carcinogenesis, for which there is no established maximum safe dose (1), and it is very difficult to standardize the necessary dose of UVB as this will vary with skin tone, season, age, body mass index (BMI), and latitude (2–6). Thus, although UV influences vitamin D status, great controversy exists regarding the optimal source for vitamin D. Although this review will present information that suggests that vitamin D has beneficial

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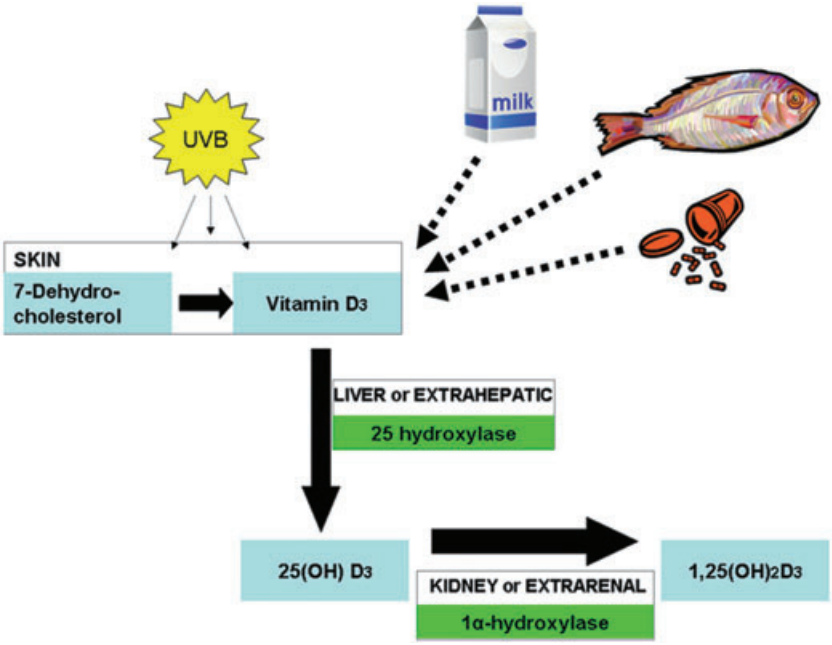

FIG. 1. Vitamin D pathway. UVB, ultraviolet B.

effects on the function of the innate immune systems, these observations should not be taken to be an endorsement of UV exposure as a means to mediate these effects.

The term "innate immunity" refers to those elements of immune protection that are genetically programmed and do not require prior exposure to pathogens for development of an effective immune response. The elements of innate immunity in the skin include the physical barrier of the stratum corneum, chemical effector molecules such as antimicrobial peptides (AMPs), danger detections systems such as the Toll-like receptors (TLRs), and cellular components that are resident or recruited to the skin to amplify responses to infection and injury [mast cells, neutrophils, and natural killer (NK) cells]. Over the last decade, it has become clear that susceptibility to infections will significantly increase without appropriate function of the innate immune system. Furthermore, as the innate immune system controls later functions of adaptive immunity, normal function of this system is essential for skin health. Elements of innate immunity play a pivotal role in skin diseases, including AD, psoriasis, connective tissue diseases, wound repair, acne, and rosacea. Thus, with recent discoveries that vitamin D controls expression of important elements of innate immunity, it is important for the dermatologist to be familiar with these issues. In the following review, we will provide an overview of central issues in the physiological functions of vitamin D with the goal of putting these issues in perspective with recent observations showing that vitamin D plays an essential and previously unappreciated function in immune defense.

Background physiology of vitamin D

Vitamin D can be produced endogenously with the help of the sun or it can be ingested orally in the form of a pill or from dietary sources. 7-Dehydrocholesterol is found in the skin and is converted to vitamin D3 or cholecalciferol upon exposure of uncovered skin to UVB radiation (280–320 nm). Vitamin D3 is then converted in the liver by 25 hydroxylase to generate 25-hydroxycholecalciferol [25(OH)D3] as demonstrated in FIG. 1. 25-Hydroxycholecalciferol is then converted into its active form, 1,25-dihydroxycholecalciferol [1,25 (OH)2D3], in the kidney by the enzyme 1α hydroxylase (7). However, this final hydroxylation step can also occur in keratinocytes when the enzyme CYP27B1 is upregulated in response to wounding or by TLR activation from microbial-derived ligands (8–10). The implications of this enzyme within keratinocytes will be discussed later.

In addition to generating vitamin D3 from the sun, it can also be ingested from pills, fortified drinks such as milk or orange juice, and, naturally, in fish or mushrooms. A serving of wild salmon can have up to 1000 IU of vitamin D3, whereas farm-

raised salmon only have a fourth as much vitamin D per serving (11). However, fish consumption is not an entirely safe way to acquire vitamin D. Fish contain mercury, which at high levels can cause neurotoxicity, and polychlorinated biphenyls, which are carcinogenic. With these risks in mind, daily consumption of fish is not recommended (12). Milk and orange juice, when fortified, can also be a good source of vitamin D, but Chen et al. found that labels often overestimated the actual vitamin D found in the drink (13). Thus, there is a scarcity of vitamin D-rich foods, and even though fish has high vitamin D levels, its consumption comes with known risks.

Current guidelines and safety

Strict guidelines for daily vitamin D intake are currently under review by the National Institute of Health, Office of Dietary Supplements. Various medical organizations including the American Academy of Dermatology (AAD) and the American Academy of Pediatrics have recently increased recommendations for vitamin D intake (14,15). These changes have been motivated by the rapidly evolving data in this field. At the present time, data are insufficient to produce a recommended daily allowance, but adequate intake for healthy people in the United States is specified as 200 IU from childhood until the age of 50, 400 IU from 51 to 70, and 600 IU for those 71 and older (16). The AAD recommends against acquiring vitamin D from unprotected exposure to the sun because of risk of skin cancer. For patients who have risk factors for vitamin D deficiency (e.g., dark skin, limited sun exposure, advanced age, BMI > 30, or photosensitivity), the AAD recommends supplementing with 1000 IU of vitamin D daily. The American Academy of Pediatrics recently increased the dose of vitamin D to 400 IU for children and adolescents who do not have adequate daily intake of vitamin D-fortified foods.

The measurement and interpretation of serum vitamin D is crucial in determining vitamin D status. Although 1,25-dihydroxycholecalciferol is the biologically active form of vitamin D, its half-life is less than 4 hours. In fact, 1,25-dihydroxycholecalciferol may remain normal or even increase in vitamin D-deficient states (17,18). Thus, serum 25-hydroxycholecalciferol with a half-life of about 2 weeks is routinely used in assessing vitamin D levels (18). The values are interpreted as follows, but may be subject to revision as further information is collected regarding effects of vitamin D on immune function:

- <20 ng/mL (<50 nmol/L) is deficient;
- 21–29 ng/mL (51–74 nmol/L) is insufficient; and
- >30 (>75 nmol/L) is sufficient (19).

With any supplement, there is concern for toxicity. Studies have indicated that vitamin D supplements are safe even at much larger doses than the highest suggested dose of 1000 IU. Maalouf et al. found that giving doses of 2000 IU to children over the period of a year did not lead to any vitamin D toxicity (20). Mocanu performed a study in which nursing home residents were given bread fortified with 5000 IU of vitamin D3. Serum vitamin D levels became sufficient, and although there were three cases of hypercalciuria, none were persistent and no renal calculi were reported (21).

Some toxicity has been reported. Jackson et al., in a trial of over 36,000 postmenopausal women, gave half of the women 1000 mg of calcium with 400 IU vitamin D and the other half ingested placebo. The women were followed on average for 7 years. Bone mineral density not only showed a slight improvement in the calcium/vitamin D group but also a slight increase in renal calculi. However, the difference between groups was very small, with 2.47% of the women in the vitamin D/calcium group experiencing renal calculi compared with 2.10% in the placebo group (hazard ratio, 0.91; 95% confidence interval, 0.83–1.01) (22). It is not clear if the use of calcium citrate instead of calcium carbonate could have prevented this slight increase in calculi (23).

UV and vitamin D

As mentioned above, UVB radiation allows for the endogenous production of vitamin D. The recommended amount of UVB exposure is much harder to determine as skin tone, season, age, BMI, and latitude affect the amount of vitamin D that will result. Harris showed that black patients have lower levels of serum 25-hydroxycholecalciferol compared with white patients at baseline. Moreover, although both white people and black people demonstrated a seasonal increase in levels from winter to summer, white people demonstrated a much greater increase in the same period (3). More recently, Armas confirmed higher levels of vitamin D in the summer compared with winter levels, and the majority of African American patients were vitamin D deficient. Armas applied UVB treatments three times per week for 4 weeks to 77 subjects who were between 19 years and 49 years of age. Patients were assigned an L value based on their skin tone, with an L value of 100 being per-

fectly white and 0 being completely black. Those with higher L values (lighter skin) had higher baseline vitamin D levels and had a greater capacity to increase serum vitamin D after receiving UVB treatments (2). Thus, both studies show that lighter skin tones require less UVB exposure to produce adequate vitamin D levels. Bogh et al. recently indicated no correlation between skin tone and vitamin D production upon exposure to UVB radiation. However, the study had a small sample size (n = 18) and made a conclusion based on a coarse division of subjects, with skin types I–IV designated as fair and skin types V and VI as dark (24). Armas' methods and results are superior based on his sample size and the use of the L value to create a spectrum of skin types rather than forcing the six Fitzpatrick skin types into one of two categories, fair and dark.

Age is also a known factor as older individuals have lower levels of 7-dehydrocholesterol, the necessary precursor for UVB-induced production of vitamin D3 (4). Even BMI has an effect as obese patients not only have lower levels of vitamin D, but also a slightly decreased rate of UV-induced production of vitamin D3 (5). Finally, as latitude increases, serum vitamin D levels decrease (6). The exact degree to which the above variables affect serum vitamin D levels is unknown. However, the correlation is known, and FIG. 2 conceptually illustrates these variables. Hopefully, future research will provide clinicians a similar diagram with actual numbers that specify whether or not supplementation with vitamin D is needed.

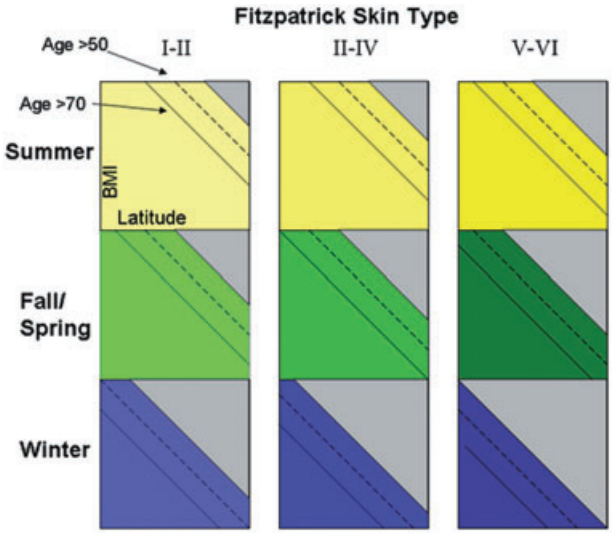

FIG. 2. Conceptual guide to vitamin D supplementation. Choose box based on patient's skin type and the current season. Next, plot a point on the diagram using the patient's body mass index (BMI) and the latitude where the patient resides. For all patients who plot in the gray area, consider supplementing. If above the solid line and age >70, consider supplementing. If above the dashed line and >50, consider supplementing.

Determining a standardized dose of vitamin D that will result from sun exposure is much more difficult than ingesting a pill of known quantity. Samanek et al. used data from Holick to deduce that exposure of 15% body surface area to 1/3–1/6 minimal erythema dose would generate 200–600 IU of vitamin D3 in individuals with Fitzpatrick skin type II (25). By using solar UV index data, the authors concluded that doses for adequate vitamin D production can occur with brief exposure that occurs incidentally to the arm, face, and hands. Their data also indicated that the difference in exposure time to produce vitamin D versus time to produce erythema shortens near noon when the sun is most intense. Thus, exposure in the morning or late afternoon affords vitamin D production with the lowest risk of UV damage (26). Unfortunately, as a controlled prospective trial to support these speculations has not been done, it is not appropriate to use this information for making solar exposure recommendations to increase vitamin D status.

An additional variable is sunscreen. Dermatologists continue to advocate its use as the same sunlight that produces vitamin D has also been designated as a carcinogen by the US Department of Health and Human Services (27). Because application of sunscreen blocks the harmful effects of UV rays, does it also block vitamin D production? In order to block vitamin D production, sunscreen would have to block 100% of UV rays. Current evidence suggests no correlation between sunscreen use and vitamin D deficiency mainly because of sunburn protective factor (SPF) properties and the improper application of sunscreen (28,29). The amount of sunscreen used for SPF determination is 2 mg/cm^2, but an observational study showed that most individuals only apply 0.5 mg/cm^2, which would reduce an SPF of 16 down to SPF 2 (30,31). Wulf also found that half of the subjects did not apply sunscreen until arrival at the beach and that sunscreen wearers reported more erythema the next day than those who did not wear sunscreen, attributable to a false sense of protection from sunscreen (30). Even if individuals applied sunscreen as directed, the highest SPF only absorbs 99% of UV radiation (1). In addition, a study by Marks compared populations using either sunscreen or placebo, and both groups experienced similar rises in serum vitamin D 1 day after sun exposure (32).

Thus, there is no basis to support speculations that vitamin D deficiency results from current sunscreen use.

The role of vitamin D in immunity as it pertains to the practicing dermatologist

Vitamin D is best known for maintaining calcium levels and maintaining healthy bones. Specifically, 1,25-dihydroxycholecalciferol increases enteral absorption of calcium, increases resorption of calcium in the renal tubules, and stimulates osteoblasts (25). The results are stronger bones, which are resistant to fracture, rickets, osteomalacia, and osteopenia/osteoporosis (7). These properties of vitamin D are the conclusions of large-scale randomized controlled trials. In contrast, most of the current information on vitamin D in dermatology comes from in vitro, animal, observational, and, only occasionally, nonrandomized trials. Thus, much of the data is preliminary and has not stood the test of a double-blinded, randomized controlled trial.

Innate immunity

An early sign of vitamin D's role in the immune system occurred as physicians observed an association of respiratory infections with rickets (33). Significant progress has occurred and continues to occur in understanding the mechanisms by which vitamin D interacts with the immune system. Vitamin D's role in the innate immune system begins at the forefront of the body's defense against pathogens, the skin. When mice were given suberythemal doses of UVB, they demonstrated an increase in AMPs and enzymes necessary for epidermal lipid synthesis as well as improved permeability barrier function indicated by a decrease in basal transepidermal water loss. When vitamin D activity was partially blocked using topical ketoconazole, AMP immunostaining showed a decrease in intensity and transepidermal water loss increased, together suggesting that it was the by-product of UVB, vitamin D, rather than the UVB itself producing these effects (34). A more recent study corroborated the importance of vitamin D in the skin as mice without the vitamin D receptor (VDR) demonstrated abnormal barrier formation, lipid secretion, and composition (35). Thus, vitamin D is one aspect of innate immunity as it enhances the capacity of the epidermis to act as an adequate barrier.

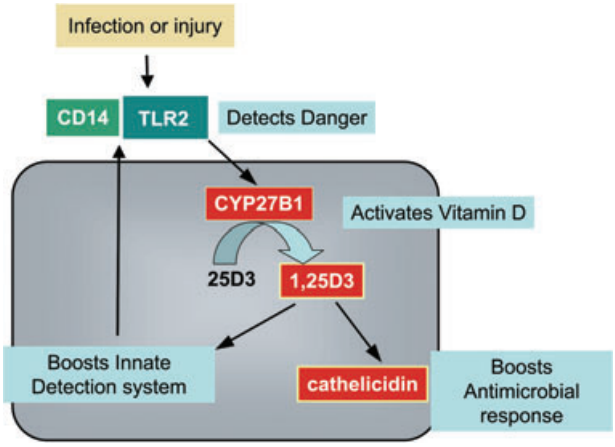

FIG. 3. Induction of vitamin D via injury or infection. TLR, Toll-like receptor.

Vitamin D's role continues once there is breakdown in the epidermal barrier. As microbial pathogens bypass a compromised epidermal barrier and are recognized by TLRs, the enzyme CYP27B1 is upregulated. Provided that adequate 25-hydroxycholecalciferol is present, then there is a site-specific increase in 1,25-dihydroxycholecalciferol, the active form of vitamin D. Upon activation, vitamin D is able to interact with the immune system through the VDR that is found in numerous cells, including T cells, B cells, NK cells, and monocytes (33). Through this VDR, vitamin D is able to induce cathelicidins, enabling them to exert an antimicrobial effect (9,36,37). Injury and inflammation of the skin also result in the induction of AMPs such as cathelicidins or defensins, which exhibit a direct antimicrobial effect as well as an ability to stimulate both the innate and adaptive immune systems (36,38,39). Thus, as illustrated in FIG. 3, the activation of 25OH D3 to 1,25D3 is linked in cells such as keratinocytes to triggers by pathogens or injury. Following local conversion to 1,25D3, there is a twofold activation of innate immunity; on the one hand, there is a local increase in the antimicrobial response, and on the other hand, 1,25D3 increases the expression of pattern recognition receptors such as TLR2 and CD14. Therefore, the cell is even better prepared to detect danger from invading pathogens.

Recent studies may indicate specifically why patients with rickets were observed to have higher rates of respiratory infections. Cathelicidin levels increased in bronchial epithelial cells from normal humans and cystic fibrosis patients when vitamin D was added in vitro. Thus, one could speculate that the lack of vitamin D in rickets patients may

have prevented an induction of cathelicidins needed in the respiratory tract to effectively prevent infection (40).

The antimicrobial effect of cathelicidins has been demonstrated often against *Mycobacterium tuberculosis*. Thus, it is no surprise that *M. tuberculosis* was historically treated with sunlight exposure when considering the causal relationship among sunlight, vitamin D production, and cathelicidin induction (41). Liu et al. have shown that the addition of 1,25-dihydroxycholecalciferol to macrophages infected with *M. tuberculosis* leads to decreased levels of viable bacilli (9). However, *M. Tuberculosis* can be a difficult organism to treat in that it is often able to evade the host's immune system inside of phagosomes (33). Vitamin D may offer a way to access this organism even within phagosomes. Yuk et al. used physiologic vitamin D levels to show that vitamin D induces the cathelicidin LL-37, which, in addition to its innate antimicrobial effect, is localized to autophagosomes to induce autophagy. Autophagy is the ingestion of sequestered material inside phagosomes by lysomes (37,42). Thus, LL-37 enables both access to and killing of *M. tuberculosis* in a vitamin D-mediated manner.

There is also clinical support of the above studies. The majority of patients with current or prior *M. tuberculosis* infection have low levels of serum vitamin D (43). Moreover, patients who receive vitamin D in addition to standard *M. tuberculosis* therapy have greater clinical improvement than those patients who receive standard therapy alone (33). Finally, there are several studies showing specific polymorphisms in the VDR gene that are associated with a change in susceptibility to *M. tuberculosis* (44,45).

AD

Patients with AD have elevated type 2 helper T cells (Th2) cytokines, such as interleukin (IL)-4 and IL-13, that are thought to prevent appropriate induction of AMPs (46). Because AD patients have lower AMP levels, they are more susceptible to bacterial and viral skin infections, of which eczema herpeticum is a particular concern (47,48). Eczema vaccinatum that can occur following smallpox vaccination in atopics may also stem from the inhibition of AMPs (46). Oral vitamin D may offer a simple way to enable AD patients to appropriately increase cathelicidin levels (49,50). Hata et al. gave an oral dose of 4000 IU of vitamin D3 daily to 14 AD patients and 14 normal controls. The AD patients experienced a sixfold increase in cathelicidin levels (50). Furthermore, keratinocytes have the ability to convert the circulating form of vitamin D, 25-hydroxycholecalciferol, to the active form, 1, 25-dihydroxycholecalciferol. Keratinocytes are able to perform this hydroxylation by the enzyme CYP27B1, which is upregulated in response to infection and wounding (8–10). The inflammatory state of atopic lesions provides the appropriate environment for CYP27B1 upregulation. Thus, when enough substrate is added to the enzyme, as in the Hata et al. study, then keratinocytes are able to produce adequate 1,25-dihydroxycholecalciferol levels to activate cathelicidins. Moreover, the increase in the active form of vitamin D does not occur systemically, but only locally when CYP27B1 is activated within keratinocytes because of infection or wounding (10). Larger scale studies will be necessary to confirm these findings.

Psoriasis

Topical vitamin D analogs have long been a useful therapy for psoriatic patients via the inhibition of keratinocyte proliferation and induction of keratinocyte differentiation. Additionally, this therapy has a mild side effect profile (51). Recent research has increased the understanding behind the therapeutic mechanism of vitamin D agents. Psoriatic lesions have increased AMP levels (unlike AD) and increased inflammatory markers IL-17A, IL-17F, and IL-8. Topical calcipotriol has recently been shown to inhibit human beta-defensin (HBD)2, HBD3, IL-17A, IL-17F, and IL-8 (52). Furthermore, mouse models have demonstrated the induction of regulatory T cells in response to both topical calcipotriol and UV radiation. These regulatory T cells are then thought to create a selective immunosuppression, leading to decreased inflammation and clinical improvement (53,54).

Skin cancer

Langberg et al. found that vitamin D has a protective effect on keratinocytes in vitro against ionizing radiation (55). Another study found that mice lacking the VDR grew tumors in response to carcinogen exposure, whereas the VDR-positive mice remained tumor free (56). Both of these studies seem to correlate with the concept that chronic sun exposure (hence, consistently elevated serum vitamin D) confers protection against melanoma (57). This same idea is perpetuated in a registry study by Tuohimaa et al. that shows a decrease in stomach, colorectal, liver, gallbladder, pancreas, lung, breast, prostate, bladder, and kidney cancers

following the diagnosis of a nonmelanoma skin cancer. Because photodamage and vitamin D production occur at the same UV wavelength, sufficient vitamin D levels may explain the decreased rates of other cancers in these patients (58). Furthermore, vitamin D supplementation compared with placebo decreases overall cancer risk. Lappe divided 1180 postmenopausal women into three groups that received daily doses of either 1100 IU of vitamin D3 and 1400–1500 mg Ca, 1400–1500 mg Ca, or placebo. After 1 year, 6.9% in the placebo group, 3.8% in the Ca group, and 2.9% in the vitamin D/Ca group developed nonskin cancers. From years 2–4, the vitamin D/Ca group fared even better, with only 2% developing nonskin cancers compared with 3.6% in the Ca group and 6.8% in the placebo group. At the end of the study, the relative risk of developing cancer compared with placebo was 0.402 ($p = 0.013$) for the vitamin D/Ca group and 0.532 ($p = 0.063$) for the Ca group (59). There may also be a role for vitamin D not just in cancer incidence, but also in cancer severity as indicated by lower levels of serum vitamin D observed in stage IV melanoma patients versus stage I (60).

The mechanism of vitamin D's protective effect on cancer may be via the VDR found in NK cells, which are known mediators of immunosurveillance (33). Although sun exposure may confer a protective effect for melanoma and many other cancers, it simultaneously promotes squamous cell carcinoma and basal cell carcinoma. Oral vitamin D offers a way to maintain sufficient serum levels without sacrificing the skin in the process.

Other potential roles of vitamin D

Numerous studies are being produced regarding potential roles of vitamin D. Although the data are exciting and intriguing, the evidence is not sufficient for clinical recommendations but only for guidance on the direction of future studies.

Although not directly related to the skin, it is important to briefly note the other proposed roles of vitamin D. Low levels of vitamin D have been found to be a risk factor for myocardial infarction (61). Aside from psoriasis, additional effects on autoimmune disease are likely as vitamin D has the potential to prevent type I diabetes mellitus (62). Also, a prospective study by Munger et al. found that women who supplemented their diet with vitamin D had a decreased risk of multiple sclerosis. This finding agrees with data that show decreased rates of multiple sclerosis closer to the equator, where UV exposure is increased, and consequently, vitamin D levels are increased (63).

Low vitamin D levels have also been associated with numerous infectious processes including periodontal disease, bacterial vaginosis, and upper respiratory tract infections (41,64,65). However, a prospective trial indicated no difference in upper respiratory tract infections for patients taking 2000 IU of vitamin D compared with placebo (66). Data also exist showing that vitamin D levels are lower in critically ill patients compared with controls or noncritically ill hospitalized patients (67,68). One study showed that giving a multivitamin to nursing home subjects 65 and older had no effect on infection rate or hospital visits. However, the multivitamin only contained 160 IU of vitamin D, and serum vitamin D was not followed (69). Although vitamin D clearly has a role in infection, larger, randomized studies are necessary to determine which infectious processes are affected by vitamin D.

Discussion

The understanding of vitamin D in human physiology has expanded tremendously in the last two decades. Although there is debate about the dosage and source of vitamin D, a more significant question must be answered regarding the incongruence of the following notions: (i) minimal UV exposure produces adequate vitamin D levels, (ii) a large number of individuals are vitamin D insufficient or deficient, and (iii) rates of skin cancer continue to increase. How can all of these statements be true? Because both vitamin D production and carcinogenesis occur via the same UV wavelength, one would expect levels of vitamin D and skin cancer to have a positive correlation. However, the Skin Cancer Foundation reports increasing skin cancer rates, whereas up to over half of the US population is vitamin D deficient (70,71). Why such a discrepancy? Assessment of serum vitamin D and assessment of cancer incidence are two very different measurements. Skin cancer rates reflect the amount of sun exposure over a period of decades, whereas vitamin D levels reflect the diet or sun exposure of an individual in the previous weeks. Thus, the discordance between vitamin D levels and skin cancer rates can even occur within a single individual if he/she had a lifetime of unprotected sun exposure but currently has low vitamin D levels because of a poor diet and a bedridden state that precludes sun exposure. A study by Johnson in 1984 may explain such high levels of

skin cancer today. His study determined that only 41% of those surveyed wore sunscreen in summer, whereas 71% had an hour or more of sun exposure each day (72). The sun exposure behavior from 25 years ago is being seen in dermatology clinics today.

Another explanation exists. Increasing skin cancer rates and an epidemic of vitamin D deficiency are not mutually exclusive if one considers that two separate groups of people are responsible for each statistic. Assuming that minimal sun exposure produces adequate vitamin D, those who comprise the vitamin D deficient group must be receiving little to no UV exposure on a daily basis. Thus, the individuals with vitamin D deficiency must be a very different population with different sun exposure behaviors than individuals who have regular sun exposure and, accordingly, adequate vitamin D levels.

Vitamin D has unquestionable merit in human physiology, and evolving studies will further define its roles. However, there are only three known choices for humans to increase their serum vitamin D levels: sun exposure, diet, and supplements. The risk of carcinogenesis from unprotected sun exposure outweighs any increase in vitamin D levels that may occur. As for diet, there are very few naturally occurring foods that contain substantial levels of vitamin D. Furthermore, one of the major dietary sources, fish, contains both mercury, which can cause neurotoxicity, and polychlorinated biphenyls, which are like the sun in their ability to be carcinogenic. The only viable option left is supplementation. Supplements provide the benefit of a known dose of vitamin D that has only limited and mild side effects. Doses of up to 5000 IU per day have been given with a very favorable benefit : risk ratio (21).

Supplementation of vitamin D may not be for every patient. However, physicians should strongly consider recommending supplementation to patients with known risk factors for vitamin D deficiency. These risk factors include darker skin tone, winter months, increasing age, elevated BMI, increased distance from the equator, and limited UV exposure. As more data are generated from larger scale and longer duration vitamin D studies, more information will become available to allow recommendations on dosing of vitamin D. The other issue that may arise is the use of vitamin D not just in low doses on a daily basis, but also in high doses when patients have *M. tuberculosis* or illnesses placing them in critical care units. Until that time, the conservative doses put forward by the National Institutes of Health (200 IU from childhood until the age of 50, 400 IU from 51–70, and 600 IU for those 71 and older) can serve as a starting point.

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