

Vitamin D and the skin: an ancient friend, revisited

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Abstract: Most vertebrates need vitamin D to develop and maintain a healthy mineralized skeleton. However, 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃], the biologically active vitamin D metabolite, exerts a multitude of important physiological effects independent from the regulation of calcium and bone metabolism. We know today that the skin has a unique role in the human body's vitamin D endocrine system. It is the only site of vitamin D photosynthesis, and has therefore a central role in obtaining a sufficient vitamin D status. Additionally, the skin has the capacity to synthesize the biologically active vitamin D metabolite 1,25(OH)₂D₃, and represents an important target tissue for 1,25(OH)₂D₃. In keratinocytes and other cell types, 1,25(OH)₂D₃ regulates growth and differentiation. Consequently, vitamin D analogues have been introduced for the treatment of the hyperproliferative skin disease psoriasis. Recently, sebocytes were identified as 1,25(OH)₂D₃-responsive target cells, indicating

that vitamin D analogues may be effective in the treatment of acne. Other new functions of vitamin D analogues include profound effects on the immune system as well as in various tissues protection against cancer and other diseases, including autoimmune and infectious diseases. It can be speculated that the investigation of biological effects of vitamin D analogues will lead to new therapeutic applications that, besides cancer prevention, may include the prevention and treatment of infectious as well as of inflammatory skin diseases. Additionally, it can be assumed that dermatological recommendations on sun protection and health campaigns for skin cancer prevention will have to be re-evaluated to guarantee a sufficient vitamin D status.

Key words: cancer – cutaneous vitamin D endocrine system – inflammatory skin diseases – skin – vitamin D – vitamin D deficiency

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The skin as a site of production of vitamin D metabolites

For more than 500 million years during evolution, phytoplankton and zooplankton have been producing vitamin D (1). While the role of vitamin D in the physiology of lower non-vertebrate organisms is not well understood, it is well known that most land vertebrates have to obtain an adequate source of vitamin D, in order to develop and maintain a healthy mineralized skeleton (1). Once vitamin D is absorbed from the diet or made in the skin by the action of sunlight (Fig. 1), it is metabolized in the liver to 25-hydroxyvitamin D [25(OH)D] and then in the kidney to 1,25-dihydroxyvitamin D [1,25(OH)₂D]. Although there are at least four different cytochrome P450 enzymes responsible for converting vitamin D to 25(OH)D, there are two principal enzymes involved in the formation of circulating 1,25(OH)₂D₃ from vitamin D: the hepatic mitochondrial vitamin D-25-hydroxylase (25OHase, CYP27A1) and the renal mitochondrial enzyme 25-hydroxyvitamin D-1 α -hydroxylase (1 α OHase, CYP27B1) for vitamin D and 25(OH)D₃, respectively (2,3). 1,25(OH)₂D is metabolized in target cells at least in part by 1,25(OH)₂D-24hydroxylase

(24OHase, CYP24A1), resulting in a specific C-24 oxidation pathway to yield the biliary excretory product calcitroic acid. These hydroxylases belong to a class of proteins known as cytochrome P450 mixed function monooxidases (2,3).

Interestingly, it has been shown that epidermal keratinocytes and various other cell types including macrophages, melanocytes, sebocytes, prostate, cutaneous squamous cell carcinomas, lung and colon cancer cells contain the enzymatic machinery needed to produce 1,25(OH)₂D₃ (Fig. 1), (4–10). The vitamin D₃ pathway in human skin is complex and characterized by photochemical activation of 7-dehydrocholesterol (7-DHC), formation of previtamin D₃, isomerization to vitamin D₃, enzymatic production of 25OHD₃, enzymatic generation of 1,25(OH)₂D₃, and finally, catabolic degradation of 1,25(OH)₂D₃. In contrast to most other cell types, epidermal keratinocytes can produce 1,25(OH)₂D₃ by two enzymatic hydroxylations of vitamin D₃. The vitamin D₃ pathway in human skin is explained in Fig. 1.

1,25(OH)₂D₃ exerts its effects via binding to a specific nuclear receptor (vitamin D receptor, VDR), a ligand-dependent transcription factor that belongs to the

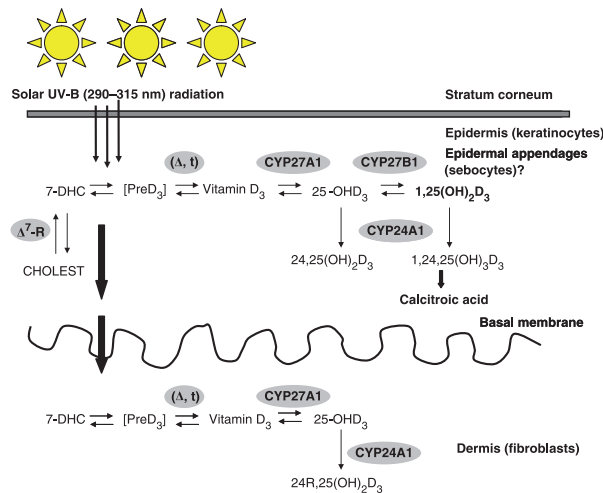


Figure 1. Vitamin D metabolism in human skin (modified from Reichrath et al. (62)). CHOLEST, cholesterol; CYP24A1, 24-hydroxylase (24OHase) for 25(OH) $_2$ D $_3$ and 1,25(OH) $_2$ D $_3$, respectively; CYP27A1, vitamin D-25-hydroxylase (25OHase); CYP27B1, 1 α -hydroxylase (1 α OHase) for vitamin D and 25(OH) $_2$ D $_3$, respectively; 7-DHC, 7-dehydrocholesterol provitamin D $_3$; PreD $_3$, previtamin D $_3$; t, temperature.

superfamily of steroid/thyroid hormone/retinoid nuclear receptors and that recognizes specific DNA sequences named vitamin D response elements (VDRE) (rev. in 5). 1,25(OH) $_2$ D $_3$ interacts with VDR in intestine and bone in order to maintain calcium homeostasis. However, the VDR is also present in a wide variety of other tissues. 1,25(OH) $_2$ D $_3$ interacts with VDR in these tissues that are not related to calcium or bone metabolism to have a multitude of other important physiological effects, that include protection against cancer and other diseases (1). It is commonly assumed that most of 1,25(OH) $_2$ D $_3$ formed by extrarenal cells act via intracrine, autocrine or paracrine mechanisms within the cells in which it is produced. In this context, the skin has a unique role for vitamin D physiology, it is a site of vitamin D and 1,25(OH) $_2$ D $_3$ synthesis and a target of biologically active vitamin D metabolites. However, it remains to be investigated to what extent epidermal synthesis of 1,25(OH) $_2$ D $_3$ modulates cellular proliferation, differentiation, apoptosis and immunological processes.

The sebaceous gland: a target for biologically active vitamin D analogues

It has been reported that incubation of the SZ95 human sebaceous gland cell line with 1,25(OH) $_2$ D $_3$ results in a dose-dependent suppression of cell proliferation (7). Using real-time PCR, it was demonstrated that key components of the vitamin D system (VDR, 25OHase, 1 α OHase, and 24OHase) are strongly expressed in SZ95 cells (7). It has

been concluded that local synthesis or metabolism of vitamin D metabolites may be of importance for growth regulation and various other cellular functions in sebaceous glands and that sebaceous glands represent promising targets for therapy with vitamin D analogues or for pharmacological modulation of calcitriol synthesis/metabolism (7).

Immunoregulation through vitamin D analogues

Effects of 1,25(OH) $_2$ D $_3$ on the immune system are pluripotent and include suppression of T-cell activation, regulation of cytokine secretion patterns, induction of regulatory T-cells, modulation of proliferation and interference with apoptosis (rev. in11) (Fig. 2). Additionally, 1,25(OH) $_2$ D $_3$ influences maturation, differentiation and migration of antigen presenting cells (11) (Fig. 2). Overall, its immunoregulatory potency is comparable with other established immunosuppressants without sharing their typical adverse effects (11). This profile makes vitamin D analogues as potential drugs for the topical or systemic treatment of immune mediated diseases including atopic dermatitis and lupus erythematosus. However, first clinical pilot studies analysing the efficacy of vitamin D analogues in the treatment of inflammatory skin diseases including atopic dermatitis were disappointing. It has to be kept in mind that vitamin D analogues exert pluripotent and dose-dependent effects on the immune system that in part may be proinflammatory. Recently, it has been shown that topical application of 1,25(OH) $_2$ D or of its low-calcemic analogue MC 903 (calcipotriol) induces thymic stromal lymphopoietin (TSLP) expression in epidermal keratinocytes, which results in an atopic dermatitis-like syndrome mimicking that seen in retinoid-X receptor (RXR) alphabeta(ep-/-) mutants and transgenic mice overexpressing

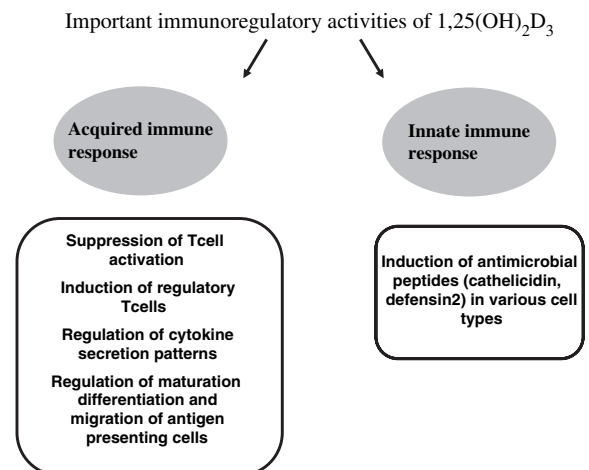


Figure 2. Immunoregulatory activities of 1,25(OH) $_2$ D $_3$.

TSLP in keratinocytes (12). Therefore, it is at present the aim to develop and characterize new vitamin D analogues with selective anti-inflammatory activity. These new compounds will hopefully be effective and safe in the treatment of inflammatory skin diseases.

Cutaneous photosynthesis of vitamin D: an evolutionary highly conserved mechanism that protects the skin against various hazards including ultraviolet-radiation and infectious diseases

Vitamin D analogues protect against oxidative stress

The activation of the stress-activated protein kinases (SAPKs), such as c-Jun N-terminal kinase (JNK) and p38, is an early cellular response to stress signals and an important determinant of cell fate. When HaCaT keratinocytes are exposed to heat shock, hyperosmotic concentrations of sorbitol, the epidermal growth factor receptor tyrosine kinase inhibitor AG1487, the proinflammatory cytokine tumor necrosis factor (TNF)- α , or H₂O₂, both SAPKs are activated (13). Pretreatment with 1,25(OH)₂D inhibits the activation of JNK by all stresses and the activation of p38 by heat shock, AG1478 and TNF- α (14). Under the same conditions, treatment with 1,25(OH)₂D protects HaCaT keratinocytes from cytotoxicity induced by exposure to H₂O₂ and hyperosmotic shock (14). It has been suggested that inhibition of SAPK activation may account for some of the well-documented protective effects of 1,25(OH)₂D on epidermal cells during exposure to ultraviolet (UV) or chemotherapy and may also be related to the anti-inflammatory actions of the hormone in skin (13). Interestingly, 1,25(OH)₂D inhibits caspase-3-like activation in HaCaT keratinocytes exposed to hyperosmotic and oxidative stresses, heat shock and TNF (14). It was shown that the hormone also protects keratinocytes from caspase-independent cell death induced by hyperosmotic and oxidative stresses.

Vitamin D analogues protect against UV-radiation

The hazardous effects of solar UV radiation, in particular of UV-B (wavelength range between 280 and 320 nm), are well recognized as the most important aetiological factor in the development of non-melanoma skin cancer (15,16). The UV-B radiation induces photochemical changes in the skin that may lead to acute effects such as sunburn and immune suppression or chronic effects like premature skin aging and skin cancer (15,16). Besides the generation of cyclobutane pyrimidine dimers (CPDs) and other DNA-photoproducts, two well-known UV-B-mediated biological effects are the induction of apoptosis (17,18) and the production of interleukin-6 (IL-6) (19). Photocarcinogenesis of skin cancer is caused largely by mutations at sites of

incorrectly repaired DNA photoproducts, of which the most common are the CPDs (16). Recently, it has been demonstrated that 1,25(OH)₂D protects primary human keratinocytes against the induction of CPDs by UV-B (17,20). This protection requires pharmacological doses of 1,25(OH)₂D and an incubation period of at least 8 h before irradiation. These data convincingly show a protective effect of vitamin D compounds against UV-B-induced photodamage. It is tempting to speculate that the UV-B-induced cutaneous production of vitamin D may represent an evolutionary highly conserved feed-back mechanism that protects the skin against the hazardous effects of solar UV-radiation.

Apoptosis, as a mode of programmed cell death, is induced following UV-B-irradiation when cellular damage is too severe to be repaired (17,18). To induce apoptosis, UV-B modulates a variety of important cellular signaling pathways that involve various nuclear and cell surface death receptors and the activation of a cascade of caspases (19). The final effector protease, caspase 3, causes cleavage of several substrates, including poly (ADPribose) polymerase (PARP), which immediately results in apoptosis (19). This cascade appears to be crucial for executing apoptosis induced by UV-B (19). UV-B-irradiation strongly induces accumulation of IL-6 mRNA and release of IL-6 protein by human keratinocytes (19). The cytokine IL-6 is an important mediator of the sunburn reaction and of UV-B-dependent immune suppression (17). Furthermore, IL-6 has been implicated in the tumorigenesis of basal cell carcinoma, a frequent neoplasm that can be induced by UV-B radiation (17,18). 1,25(OH)₂D protects human skin cells from UV-induced cell death and apoptosis (17–19). Using an ELISA that detects DNA-fragmentation, it was shown that pretreatment with 1,25(OH)₂D suppresses UV-B-induced apoptotic cell death by 55–70% (19). Pretreatment with 1,25(OH)₂D also inhibits mitochondrial cytochrome *c* release (90%), a hallmark event of UV-B-induced apoptosis (19). Furthermore, 1,25(OH)₂D reduces JNK activation and IL-6 production (19). Additionally, pretreatment of keratinocytes with 1,25(OH)₂D efficiently, but not completely, inhibits UV-B-induced PARP-cleavage (19). Recently, the anti-apoptotic effect of 1,25(OH)₂D in keratinocytes was confirmed, using cisplatin and doxorubicin as apoptotic triggers (18). In that study, 1,25(OH)₂D activated two independent survival pathways in keratinocytes: the MAPK/ERK kinase (MEK)/extracellular signal regulated kinase and the phosphatidylinositol 3-kinase (PI-3K)/Akt pathway (18). Additionally, 1,25(OH)₂D changes the expression of several apoptosis regulators belonging to the Bcl-2 family. Treatment with 1,25(OH)₂D, increases levels of the anti-apoptotic protein Bcl-2 and decreases levels of the proapoptotic proteins Bax and Bad in a time- and dose-dependent way (18). Taken together, these findings

suggest the existence of a photoprotective effect of active vitamin D analogues and create new perspectives for the pharmacological use of active vitamin D compounds in the prevention of UV-B-induced skin damage and carcinogenesis (17–21). However, one has to remember that the physiological consequences of $1,25(\text{OH})_2\text{D}$ -mediated inhibition of cell death and apoptosis are not well understood and under distinct circumstances, may have contrary effects and even favour the photocarcinogenesis of skin cancer.

Vitamin D analogues protect against infectious agents

Recently, it has been shown that $1,25(\text{OH})_2\text{D}$ represents a direct regulator of antimicrobial innate immune responses (22–26). The innate immune system of mammals provides a rapid response to repel assaults from numerous infectious agents including bacteria, viruses, fungi and parasites. A major component of this system is a diverse combination of cationic antimicrobial peptides (AMPs) that include the α - and β -defensins and cathelicidins (22). Because bacteria have difficulty developing resistance against AMPs and are quickly killed by them, this class of antimicrobial agents is being commercially developed as a source of peptide antibiotics (22). Cathelicidins are a class of mammalian AMPs expressed in leukocytes and at epithelial surfaces (27). Human cathelicidin AMP hCAP18 is encoded by *CAMP* on chromosomal location 3p21 and is the sole cathelicidin protein in humans. The cathelicidins are characterized by a C-terminal cationic AMP domain that is activated by cleavage from the N-terminal cathelin portion of the propeptide. The majority of the *CAMP* propeptide is stored in secondary or specific granules of neutrophils from which it can be released at sites of microbial infection (22). In addition to neutrophils, various white blood cell populations express hCAP18. These include natural killer cells, T cells, B cells, monocytes and mast cells (22). The *CAMP* is synthesized and secreted in significant amounts by those tissues that are exposed to environmental microbes. This includes the squamous epithelia of the mouth, tongue, oesophagus, lungs, intestine, cervix and vagina (22). In addition, it is produced by salivary and sweat glands, epididymis, testis and mammary glands (22). Expression in these tissues results in secretion of the polypeptide in wounds, sweat, airway surface fluids, seminal plasma and milk (22). Recent studies have shown that cathelicidins, in addition to being antimicrobial, are multifunctional proteins with receptor-mediated effects on eukaryotic cells and activity in chemotaxis, angiogenesis and wound healing (27,28). In the skin, there is low constitutive expression of hCAP18 in the basal layer of keratinocytes but rapid upregulation upon inflammation and injury (29–31). The possibility of extrinsically manipulating endogenous expression of *CAMP* for systemic and localized therapeutic benefit is

very attractive. Because AMPs serve a role in host defense and may act as mediators of other biological processes, their expression is tightly regulated. Molecular mechanisms controlling the expression of *CAMP* are still poorly understood. Interestingly, the promoters of the human *camp* and defensin 2 (*defB2*) genes contain consensus VDRE that mediates $1,25(\text{OH})_2\text{D}$ -dependent gene expression (23). $1,25(\text{OH})_2\text{D}$ induces antimicrobial peptide gene expression in isolated human keratinocytes, monocytes and neutrophils and human cell lines, and $1,25(\text{OH})_2\text{D}$ along with lipopolysaccharide (LPS) synergistically induce *camp* expression in neutrophils (23). Moreover, $1,25(\text{OH})_2\text{D}$ induces increases in antimicrobial proteins and secretion of antimicrobial activity against pathogens including *Pseudomonas aeruginosa* (23). Weber et al. (24) convincingly demonstrated in human keratinocytes an upregulation of *CAMP* by treatment with 100 nM $1,25(\text{OH})_2\text{D}$ or MC 903 (calcipotriol). $25(\text{OH})\text{D}_3$, the precursor of biologically active $1,25(\text{OH})_2\text{D}$, stimulated *CAMP* expression at the same magnitude as $1,25(\text{OH})_2\text{D}$ or MC 903. In this study, all compounds were active down to levels of 10 nM while the precursor of vitamin D biosynthesis, 7-DHC, was ineffective at all concentrations tested (24). Western blot analysis of independent investigations confirmed that the elevated transcription of *CAMP* was reflected on the protein level (22,24). The induction of *CAMP* expression occurred via a consensus VDRE in the *CAMP* promoter that was bound by the VDR. Induction of *CAMP* in murine cells was not observed and expression of *CAMP* mRNA in murine VDR-deficient bone marrow was similar to wild-type levels (22). Comparison of mammalian genomes revealed evolutionary conservation of the VDRE in a short interspersed nuclear element or SINE in the *CAMP* promoter of primates that was absent in the mouse, rat and canine genomes (22). In conclusion, there is convincing evidence that $1,25(\text{OH})_2\text{D}$ and analogues directly regulate antimicrobial peptide gene expression in humans, revealing the potential of these compounds for the treatment of opportunistic infections. In innate immune responses, activation of Toll-like receptors (TLRs) triggers direct antimicrobial activity against intracellular bacteria, which in murine, but not human, monocytes and macrophages is mediated principally by nitric oxide (25). The TLR activation of human macrophages up-regulates expression of the VDR and the vitamin D- $1\alpha\text{OHase}$ (*CYP27B1*) genes, leading to induction of cathelicidin and killing of intracellular *Mycobacterium tuberculosis*. In that study, sera from African-American individuals, who were known to have increased susceptibility to tuberculosis, had low $25(\text{OH})\text{D}_3$ and were inefficient in supporting cathelicidin messenger RNA induction. These data support a link between TLRs and vitamin D-mediated innate immunity and suggest that differences in ability of human populations to produce vitamin D may contribute

to susceptibility to microbial infection (25). It has been reported that vitamin D deficiency predisposes children to respiratory infections and that volunteers inoculated with live attenuated influenza virus are more likely to develop fever and serological evidence of an immune response in the winter (32). The UV-radiation (either from artificial sources or from sunlight) reduces the incidence of viral respiratory infections, as does cod liver oil (which contains vitamin D). An interventional study showed that vitamin D reduces the incidence of respiratory infections in children and it has been concluded that a lack of vitamin D may be of importance for the remarkable seasonality of epidemic influenza (Hope-Simpson's 'seasonal stimulus', 32). Taken these data together, the effects of solar UV radiation on the immune system are not exclusively immunosuppressive, but may even stimulate distinct immune responses.

The skin as a key tissue for the health of the human body – the serious health problem of vitamin D deficiency

Our knowledge about new important physiological effects of vitamin D metabolites is growing rapidly. Of high importance was the discovery that in contrast to earlier assumptions, skin, prostate, colon, breast and many other tissues express the enzyme to convert 25(OH)D to its active form, 1,25(OH)₂D (1,4–8,33). The insights into new biological functions of 1,25(OH)₂D in regulating cell growth, modulating the immune system and the renin–angiotensin system have provided explanations for why reduced sun exposure at higher latitudes is associated with a broad variety of diseases, including an increased risk of dying of many types of cancers, developing type 1 diabetes and multiple sclerosis and having a higher incidence of hypertension (Fig. 3) (rev. in 1, 34). Most humans obtain their

vitamin D requirement from exposure to sunlight (19). Estimates of between 80% and 100% of the vitamin D needed by humans come from the exposure to sunlight (1), although adequate levels of 25(OH)D can be obtained by oral supplementation with vitamin D. A connection between vitamin D deficiency and various diseases including multiple types of cancer (e.g. colon-, prostate- and breast cancer) has been confirmed in a large number of studies (34–39). In the US, the annual numbers of premature deaths from cancer that are associated with lower UV-B exposures have been estimated to be 21 700 [95% confidence interval (CI), 20 400–23 400] for white Americans, 1400 (95% CI, 1100–1600) for black Americans, and 500 (95% CI, 400–600) for Asian-Americans and other minorities (38). The idea that sunlight and vitamin D inhibit the growth of human cancers is not new. In 1915, Hoffman evaluated for the first time cancer mortality and latitude (40). In 1936, Peller reported an apparent deficit of non-skin cancer among US Navy personnel, who experienced an excess of skin cancer, and concluded that skin cancers induce a relative immunity to other types of cancer (41). Consequently, he recommended the deliberate induction of non-melanoma skin cancers, which were easily to detect and to treat, as a form of vaccination against more life-threatening and less treatable cancers. In 1941, the pathologist Frank Apperly published geographic data that demonstrated an inverse correlation between levels of UV-radiation in North America and mortality rates from non-skin cancers (42). Since the time of Hoffman's and Apperly's first reports, an association between increased risk of dying of various internal malignancies (e.g. breast, colon, prostate and ovarian cancer) and decreasing latitude towards the equator has now been confirmed (38). A correlation of latitudinal association with sun exposure and decreased 25(OH)D serum levels has been demonstrated (35–38). Interestingly, black men, who have an increased risk to develop vitamin D deficiency, have also an increased risk of prostate cancer and develop a more aggressive form of the disease. Moreover, it has been reported that sun exposure is associated with a relatively favourable prognosis and increased survival rate in various other malignancies, including malignant melanoma (43–46). It has been speculated that these findings were related to UV-exposure-induced relatively high serum levels of vitamin D. Berwick et al. (43) recently evaluated the association between measures of skin screening and death from cutaneous melanoma in case subjects ($n = 528$) from a population-based study of cutaneous melanoma, who were followed for an average of more than 5 years. They found that sunburn, high intermittent sun exposure and solar elastosis were statistically significantly inversely associated with death from melanoma and concluded that sun exposure is associated with increased survival from melanoma (43). Cell and animal

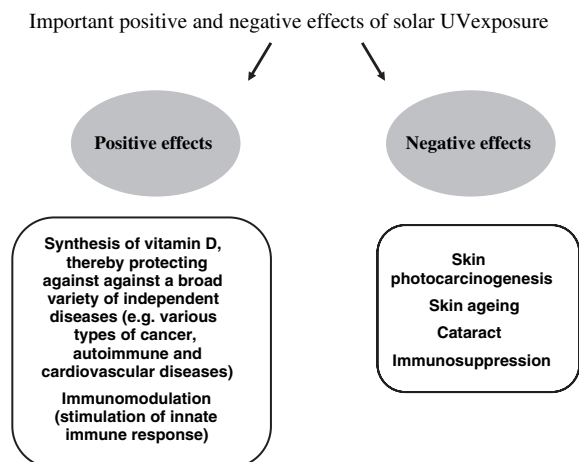


Figure 3. Positive and negative effects of solar UV exposure.

experiments reported in the literature, as well as epidemiological data from some countries relate survival of various malignancies including colon cancer with sun exposure, latitude and vitamin D₃ synthesis in skin (43–46).

Rigorous sun protection increases the risk of vitamin D deficiency

We analysed whether patients who need to protect themselves for medical reasons from solar UV-exposure are at risk to develop vitamin D deficiency (47,48). For renal transplant recipients frequently have to take immunosuppressive medications that are well known to increase the risk to develop UV-induced skin cancer, it is of high importance that these patients protect themselves against solar UV-exposure. Serum 25(OH)D₃ levels were investigated in renal transplant patients with adequate renal function and in an age- and gender-matched control group ($n = 31$), at the end of winter (February/March) (47). All renal transplant recipients had practised solar UV-protection after transplantation. Serum 25(OH)D₃ levels were significantly lower in renal transplant patients as compared with matched (age and gender) controls ($P = 0.007$). Geometrical mean (with 95% CI) in renal transplant recipients was 10.9 ng/ml (8.2–14.3) compared with 20.0 ng/ml (15.7–25.5) in controls (47). In another pilot study, we investigated basal 25(OH)D₃ serum levels in a small group of patients with xeroderma pigmentosum (XP, $n = 3$) or basal cell nevus syndrome (BCNS, $n = 1$) at the end of winter (48). The 25(OH)D₃ levels in all four patients were markedly decreased with a mean value of 9.5 ng/ml (normal range: 15.0–90.0 ng/ml). In conclusion, we have demonstrated that patients who protect themselves against solar UV-exposure are at risk to develop vitamin D deficiency (47,48).

How much vitamin D do we need?

How much vitamin D do we need to achieve a protecting effect against cancer and other diseases? The US Recommended Dietary Allowance (RDA) of vitamin D from 1989 is 200 IU (49). Yet, studies have shown that 200 IU/day has no effect on bone status (49,50). It has been recommended that adults may need, at a minimum, five times the RDA, or 1000 IU, to adequately prevent bone fractures, protect against some cancers and derive other broad-ranging health benefits (49–51). In a recent quantitative meta analysis, a 50% lower risk of colorectal cancer was associated with a serum 25(OH)D level ≥ 33 ng/ml, compared with ≤ 12 ng/ml (51). In conclusion, the 1989 US RDA of 200 IU is antiquated, and the newer 600 IU US Daily Reference Intake dose for adults older than 70 is still not adequate (49,50,52–55). It has been speculated that even the

2000 IU upper tolerable intake, the official US safety limit, does not deliver the amounts of vitamin D that may be optimal (49,50,52–55). To raise 25(OH)D serum levels from 50 to 80 nm/l, it requires an additional intake of approximately 1700 IU vitamin D per day (56). On a sunny summer day, total body sun exposure produces approximately 10 000 IU vitamin D per day (55). As a result, concerns about toxic overdose with dietary supplements that exceed 800 IU are poorly founded. It has been speculated that a person would have to consume almost 67 times more vitamin D than the current 600 IU recommended intake for older adults to experience symptoms of overdosage (49). Vieth (49) believes people need 4000–10 000 IU vitamin D daily and that toxic side effects are not a concern until a 40 000 IU/day dose. Today, it is a matter of debate how much vitamin D is necessary. Most experts agree that daily doses of at least 1000 IU are needed to achieve a protecting effect against cancer and other diseases (49,50,52–55,57,58). However, some experts expressed concern that patients with chronic granulomatous diseases could potentially develop hypercalciuria and hypercalcemia, if they took 2000–4000 IU of vitamin D per day. In a recent review, leading experts in the field concluded that the evidence to date suggests that daily intake of 1000–2000 IU/day of vitamin D₃ could reduce the incidence of colorectal with minimal risk (51).

In conclusion, dermatologists and other physicians have to be aware that strict sun protection to prevent skin cancer may induce the severe health risk of vitamin D deficiency. To guarantee a sufficient vitamin D status, dermatological recommendations on sun protection and health campaigns for skin cancer prevention will have to be re-evaluated (58). There is no doubt that UV radiation is mutagenic and is the main reason for the development of non-melanoma skin cancer. Therefore, excessive sun exposure has to be avoided, particularly burning in childhood. To reach this goal, the use of sunscreens as well as the wearing of protective clothes and glasses is absolutely important. Additionally, sun exposure around midday should be avoided during the summer in most latitudes. However, the dermatological community has to recognize that there is convincing evidence that the protective effect of less intense solar radiation outweighs its mutagenic effect. In consequence, many lives could be prolonged through careful exposure to sunlight or more safely, vitamin D supplementation, especially in non-summer months. As Michael Holick reported previously (59,60), we have learned that at most latitudes such as Boston, USA, very short and limited solar exposure is sufficient to achieve 'adequate' vitamin D levels. Exposure of the body in a bathing suit to one minimal erythemal dose (MED) of sunlight is equivalent to ingesting about 10 000 IU of vitamin D, and it has been reported that exposure of less than 18%

of the body surface (hands, arms, and face) two to three times a week to a third to a half of an MED (about 5 min for skin-type-2 adult in Boston at noon in July) in the spring, summer and autumn is more than adequate (58–60). Anyone intending to stay exposed to sunlight longer than recommended above should apply a sunscreen with a sufficient sun-protection factor to prevent sunburn and the damaging effects of excessive exposure to sunlight. Although further work is necessary to define the influence of vitamin D deficiency on the occurrence of melanoma and non-melanoma skin cancer, it is at present mandatory that especially dermatologists strengthen the importance of an adequate vitamin D status if sun exposure is seriously curtailed. It has to be emphasized that in people who are at high risk of developing vitamin D deficiency (e.g. nursing-home residents; patients with skin type I or patients under immunosuppressive therapy who must be protected from the sun exposure), vitamin D status should be monitored subsequently. Vitamin D deficiency should be treated, for example, by giving vitamin D orally as recommended previously (58). It has been shown that a single dose of 50 000 IU vitamin D once a week for 8 weeks is efficient and safe to treat vitamin D deficiency (rev. in 58). An alternative to prevent vitamin D deficiency would be the use of vitamin D containing ointments or the supplementation of foods with vitamin D. However, it should be noted that vitamin D containing ointments are, at least in Europe, not allowed as cosmetics. These antiquated laws are the result of the fear of vitamin D intoxication that was evident in Europe in the 1950s (61) and should be re-evaluated, for they do not reflect our present scientific knowledge. If we follow the guidelines discussed above carefully, they will ensure an adequate vitamin D status, thereby protecting us against adverse effects of strict UV protection recommendations. Most importantly, these measures will protect us sufficiently against the influence of vitamin D deficiency on the occurrence of various independent diseases including malignancies without increasing our risk to develop UV-induced skin cancer. It is of high importance that dermatologists and other clinicians are aware of the severe health problems related to vitamin D deficiency.

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