ABSTRACT

Vitamin D, originally associated with rickets and osteomalacia, has recently been shown to have a role in a number of medical and dermatological diseases. It has been found that vitamin D receptors and the enzymatic machinery capable of converting circulating 25-hydroxyvitamin D [25(OH)D] to the active 1,25-hydroxyvitamin D [1,25(OH)2D] is present in most cells in the body including the skin. It is well known that vitamin D analogs are effective in the treatment of psoriasis vulgaris because of their anti-proliferative and pro-differentiating effects on keratinocytes. However, new roles have been found for vitamin D in skin, such as immunomodulatory and anti-apoptotic effects thus raising a possibility of its use in conditions such as atopic dermatitis and infections. Increasing evidence now indicates that cutaneous vitamin D synthesis may help in prevention of skin malignancies and further, that cancer mortality may be reduced by oral supplementation of vitamin D. Various epidemiological studies have linked low levels of vitamin D to autoimmune diseases including vitiligo, and topical vitamin D has been used to treat vitiligo. This review focuses on a wide array of roles of vitamin D in various skin disorders with emphasis on both its well-established role as in psoriasis and the less characterized role in other disorders such as ichthyosis, tuberculosis or acne.

Key words: Ichthyosis, psoriasis, vitamin D, vitiligo

INTRODUCTION

Vitamin D, also known as the sunshine vitamin, has been recently implicated in a plethora of medical illnesses. Decrease in incidence of rickets after fortification of foods with vitamin D led physicians to believe that vitamin D related health disorders had come to an end. But unfortunately, rickets appears to be a mere drop in the vast ocean of disorders resulting from vitamin D deficiency.

Adequate sunlight and a diet rich in oily fish and fortified milk are the major sources of vitamin D for humans. Vitamin D functions like a hormone and regulates parathyroid hormone (PTH), calcium and phosphorous metabolism leading to important implications for the integrity of the skeletal system. The discovery of vitamin D receptors (VDRs) in most cells of the body and the presence of enzymes that synthesize the active form of vitamin D, namely 1,25-dihydroxyvitamin D [1,25(OH)2D] in non-renal sites like skin have led to a renewed interest in its functions,[1] particularly its role in decreasing the risk of several chronic, highly morbid conditions such as carcinomas, autoimmune diseases, infectious diseases, and cardiovascular diseases.[1]

The cutaneous synthesis of vitamin D and its role in the treatment of certain common skin disorders like psoriasis has made it an important topic for dermatologists. Studies that point towards a role of vitamin D as an immunomodulator have opened channels to discover its therapeutic effects in atopic dermatitis, psoriasis, and skin cancer.[2]
THE CUTANEOUS BIOSYNTHESIS PATHWAY OF VITAMIN D3

Pro-vitamin D3 or 7-dehydrocholesterol, which is primarily found in the basal and spinous cell layers of the epidermis, undergoes a photochemical reaction to form pre-vitamin D3. The UV light blocking function of melanin leads to a requirement of greater UV light exposure in order to produce equivalent amounts of Vitamin D3 in dark skinned populations. Figure 1 shows the vitamin D3 pathway in human skin. In addition to its action on the kidneys, calcitriol bound to vitamin D binding protein acts by both genomic and non-genomic mechanisms on certain other target tissues like bone, intestine, and parathyroid gland that express the vitamin D receptors.

EFFECTS OF CALCITRIOL ON CUTANEOUS BIOLOGY

Calcitriol synthesized in the keratinocytes regulates their growth, differentiation, apoptosis and other biological processes via intracrine, autocrine and paracrine effects on the epidermal cell population.

Effects on keratinocytes
Vitamin D leads to stimulation of in vitro keratinocyte proliferation at low concentrations and its inhibition at higher concentrations (≥10⁻⁸ M).

Effects on skin immune system
Various immunological cells such as monocytes, T and B lymphocytes and Langerhans cells express both vitamin D receptor and 25-hydroxy-vitamin D-1α-hydroxylase implicating a vital role of vitamin D in control and regulation of immune mechanisms.

Effects on keratinocyte apoptosis
Calcitriol causes stimulation of ceramide synthesis by inducing the neutral Mg²⁺-dependent sphingomyelinase (thereby increasing the conversion of sphingomyelin to ceramide) and in return, ceramide enhances the pro-differentiating effect of calcitriol on keratinocytes in a feedback loop. Whereas pharmacological levels of calcitriol induce apoptosis of keratinocytes and other epidermal cells, physiological levels block the effect of pro-apoptotic ceramides, UV radiation and tumor necrosis factor-α (TNF-α).

| Table 1: Immunomodulatory effects of vitamin D |
|-----------------|-------------------------|
| Cell type       | Effect of vitamin D     |
| T cells         | Inhibits activation     |
| CD25+/CD4+ T cells | Induces generation of |
|                 | tolerance and inhibits immunity after stimulation with antigen |
| Dendritic cells | Suppresses the expression of MHC class II molecules and co-stimulatory molecules like CD40, CD80, and CD86 |
| Keratinocytes and myeloid cells | Major regulator of AMPs |

AMPs: Antimicrobial peptides, MHC: Major histocompatibility complex, CD: Cluster of differentiation, IL: Interleukin
**Effect as an antioxidant**

The generation of an antioxidant in keratinocytes *in vitro* may explain the photoprotection that vitamin D offers against harmful oxygen radicals induced by exposure to UVB.

**ROLE OF VITAMIN D IN SKIN DISEASES**

**Vitamin D and psoriasis linkage**

In spite of the well established role of topical vitamin D analogs in psoriasis, the precise mechanisms underlying their therapeutic effectiveness are still not completely understood. Modulation of various markers of epidermal proliferation, proliferating cell nuclear antigen (PCNA) and Ki-67 antigen, and differentiation (involucrin, transglutaminase K, filaggrin, cytokeratins 10, 16) has been shown *in situ* in lesional psoriatic skin following topical application of vitamin D analogs.[13] However, topical vitamin D does not help much in reducing dermal inflammation (cluster of differentiation (CD-) antigens, cytokines, HLA-DR, etc) seen in psoriasis due to reduced bioavailability of topical preparations in the dermis.[13]

The therapeutic effects of topical vitamin D occur via a vitamin D receptor mediated genomic mechanism resulting in inhibition of keratinocyte proliferation.[14] Non-genomic mechanisms induce keratinocyte differentiation by increasing intracellular calcium levels.[15] Besides this, inhibition of T cell differentiation and proliferation in response to interleukin 1 (IL-1) by vitamin D decreases immunoglobulin production. The anti-inflammatory effects may also result from inhibition of production of IL-2, IL-6, and interferon-gamma (IFN-γ). Further, topical calcipotriol inhibits human beta defensin (HBD)2, HBD3, IL-17A, IL-17F, and IL-8 which are found in increased levels in psoriatic lesions,[16] thus blocking the cathelicidin pathway, reducing inflammation and reversing some of the changes that occur in psoriatic lesion.

The correlation of the clinical improvement with increased vitamin D receptor mRNA in vitamin D–treated cutaneous lesions,[17] has led to the categorization of “responders” and “non-responders” with the former showing an increase in vitamin D receptor mRNA in treated skin areas.[14] Allelic variations in individual vitamin D receptor genes may also determine response to treatment. An increased association of the A allele for the vitamin D receptor was found in patients with psoriasis.[18] According to Colin et al., the FokI polymorphism is associated with the response to calcipotriol. However, other studies have shown that distinct vitamin D receptor genotypes are not associated with clinical response to calcipotriol.[13] Studies on the serum levels of 1,25(OH)2D or 25(OH)D in psoriatic patients have shown conflicting results, with some showing reduced levels of 1,25(OH)2D in patients with manifest psoriasis.[19] Besides, the coincidence of pustular psoriasis with hypocalcemia[20] and exacerbation of psoriasis with chloroquin therapy (mediated via reduction in 1,25(OH)2D levels due to inhibition of 1α-(OH)ase (CYP27B1)) are well known.[21]

Improvement of psoriasis with sun exposure initiated the oral use of 1,25-dihydroxyvitamin D (calcitriol) as a therapeutic option.[13] In 1985, MacLaughlin et al. speculated that oral calcitriol may be effective in the treatment of psoriasis.[22] In the same year, Morimoto and Kumahara reported remission of psoriatic skin lesions in a patient of osteoporosis who was treated with oral 1α-(OH)D3.[23] Unfortunately, the oral use of vitamin D is limited due to the risk of adverse effects such as hypercalcemia, hypercalciuria, nephrocalcinosis, nephrolithiasis and reduction in bone mineral density secondary to its calcemic effect.[13]

But a recent review shows that hypercalcemia can be easily monitored and is avoidable with proper dosing and monitoring. A correlation between low levels of serum vitamin D and increased severity of psoriasis has also been documented in the literature.[24] Further, with the growing evidence that psoriasis is a systemic disease that affects many organ systems and results in comorbidities, there is an urgent need for re-evaluation of the role of oral vitamin D in the treatment of psoriasis. Perez and colleagues[25] observed improvement with oral vitamin D in 88% of 85 patients with psoriasis; 26.5% had complete clearance, 36.2% had moderate improvement and 25.3% had slight improvement. Gaal et al.[26] observed a significant immunomodulatory effect of systemic alphacalcidol [1α-(OH)D3] on patients with psoriatic arthropathy and proposed it as a valuable therapeutic alternative. Another study demonstrated that a combination of acitretin and oral calcitriol resulted in a faster reduction of PASI (Psoriasis Area Severity Index) in patients of chronic plaque psoriasis.[27] Published reports suggest that oral vitamin D through its anti-inflammatory action also improves the metabolic syndrome and cardiovascular disease which may be associated with...
psoriasis.[24] Larger studies should be undertaken with this inexpensive and easily available option in the management of psoriasis and the associated metabolic syndrome.

Topical calcitriol with its minimal effects on serum calcium has been approved by the US Food and Drug Administration (USFDA) for the treatment of psoriasis. The effectiveness and safety of various vitamin D analogs including calcitriol, calcipotriol, tacalcitol, hexafluoro-1,25-dihydroxyvitamin D3 and maxacalcitol in the topical treatment of psoriasis have been documented in several studies.[13] They are more efficacious with superior cosmetic acceptability than the earlier topical treatments such as tar and dithranol and have potency comparable to mid-potency topical corticosteroids.[28]

Lack of skin atrophy or adrenal suppression is another reason for their inclusion in the therapeutic armamentarium for psoriasis.[28]

The role of various available topical vitamin D analogs[28] is presented in Table 2. Combined topical treatment with calcipotriol ointment (50 μg/g) and betamethasone ointment was shown to be less irritating and slightly more effective than calcipotriol used alone.[29] As a rule, the use of calcipotriol ointment on face and flexures should be avoided due to its irritancy. Scalp psoriasis responds well to calcipotriol solution without side effects. Therapeutically resistant areas like nails have been reported to have responded to calcipotriol ointment but there have been no consistently effective treatment for psoriatic nails up till now.[28]

Kragbelle and coworkers observed that topical application of calcipotriol ointment (any time upto 2 hours before or immediately after) with simultaneous UV-B phototherapy caused an improvement in the psoriatic lesions, possibly due to increased cutaneous vitamin D synthesis.[30] Combination therapy with agents like TNF-α inhibitors, methotrexate (MTX), low-dose oral cyclosporine (2 mg/kg/day), oral acitretin, topical dithranol and topical steroids may enhance the therapeutic efficacy of topical vitamin D.[31-36]

Psoriasis is a chronic condition with frequent relapses and may require life long intermittent therapy.

It is now accepted that vitamin D analogs are effective and safe for the topical treatment of skin areas that are usually difficult to treat and that respond slowly. They do not exhibit tachyphylaxis and topical treatment can be continued indefinitely. Also, they are effective in the treatment of psoriatic skin lesions in children and in HIV patients.[28]

Vitamin D and atopic dermatitis

As vitamin D has the potential to suppress inflammatory responses, enhance antimicrobial peptide activity and promote the integrity of the permeability barrier, vitamin D supplementation provides a possible therapeutic intervention for atopic dermatitis. The role of vitamin D in the pathogenesis of atopic dermatitis has not been fully established. An observational study of 138 Norwegian patients with atopic dermatitis did not find any correlation between low dietary vitamin D and clinical disease severity scores.[37] A small pilot study showed a non-significant benefit of vitamin D supplementation in seasonal atopic dermatitis.[38] A study has shown that a higher intake of vitamin D in early life is associated with greater prevalence of atopic manifestations. This was in support of prior studies suggesting a role of vitamin D intake during infancy in the development

<table>
<thead>
<tr>
<th>Vitamin D analog</th>
<th>Type of analogue</th>
<th>Use in psoriasis</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitriol</td>
<td>Natural analog, can be used topically as monotherapy or in combination</td>
<td>Maximum dose of ointment should not exceed 200 g/week</td>
<td>Not much. No risk of hypercalcemia even with prolonged twice-daily application. Calcitriol ointment should not be used for oral, ophthalmic or intravaginal use, and has not been studied in pregnant or nursing women[29]</td>
</tr>
<tr>
<td>Calcipotriene</td>
<td>Synthetic analog</td>
<td>One of the most commonly prescribed medications. Applied twice daily up to 100 g/week, it is slightly more effective than betamethasone-17-valerate</td>
<td>Has less than 0.05% of the effect of vitamin D on calcium metabolism. Cutaneous irritation seen in 20% cases in intertriginous areas and face</td>
</tr>
<tr>
<td>Maxacalcitol</td>
<td></td>
<td>It is more effective than once-daily application of calcipotriene</td>
<td>Burning sensation in the lesions may require discontinuation of therapy</td>
</tr>
<tr>
<td>Tacalcitol</td>
<td></td>
<td>Well tolerated</td>
<td>Cutaneous irritation in 5.9% cases</td>
</tr>
</tbody>
</table>
of atopic allergy later in childhood. On the contrary, some epidemiological studies have demonstrated that patients with atopic dermatitis have a lower vitamin D intake when compared with controls.

Several recent reports have shown that vitamin D plays a role in the pathogenesis of atopic dermatitis through its immunomodulatory properties. Schaubet al. demonstrated that the active form of vitamin D [1,25(OH)2D3] enhanced the expression of antibacterial peptides and thus prevented skin infections. Liu et al. demonstrated a link between vitamin D-mediated activation of toll-like receptors, the production of cathelicidin and diminished sensitivity to bacterial infections. Depending on the concentration, vitamin D can stimulate or inhibit keratinocyte differentiation[6] and stimulate synthesis of proteins such as filaggrin that are necessary for formation of the stratum corneum barrier.[42] Further, it has been demonstrated that vitamin D analogs suppress in vitro immunoglobulin E (IgE) production and IgE-mediated cutaneous reactions.[43] Ong et al. demonstrated significantly decreased immunostaining for cathelicidins (LL-37) in acute and chronic atopic dermatitis lesions compared to psoriatic skin lesions.[44] This finding may explain the differences in skin infections between patients with these two diseases. Among patients with atopic dermatitis, those with a history of herpes simplex virus (HSV) superinfection have significantly lower cathelicidin levels. Antiviral assays have shown that cathelicidin has activity against herpes simplex virus.[45]

The various studies evaluating the role of vitamin D in atopic dermatitis have been tabulated in Table 3. The results of these studies indicate that vitamin D supplementation may have a therapeutic role in the disease with a good safety profile. However, further trials involving larger sample sizes and longer treatment periods will be necessary to more fully assess vitamin D as a therapeutic strategy in atopic dermatitis.

**Vitamin D and vitiligo**

Autoimmunity plays an important role in pathogenesis of vitiligo which is also evident by coexistence of various autoimmune disorders with vitiligo. In turn, vitamin D levels have been found to be reduced in various autoimmune disorders, thus pointing to a plausible association between vitiligo and vitamin D levels. However, the exact mechanism by which vitamin D effects autoimmunity is still an enigma.

Some studies have investigated the association between vitiligo and 25(OH)D levels. In the study by Silverberg et al., decreased levels of 25(OH)D were found in patients with vitiligo with additional autoimmune diseases and in another study by Li et al., statistically significantly decreased levels of 25(OH)D were seen in patients with vitiligo as compared to controls, thus suggesting that a deficiency in 25(OH)D may be a contributing factor in the development of vitiligo.

The use of vitamin D analogs in combination with PUVA sol for the treatment of vitiligo was first reported by Parsad et al. Subsequently, topical vitamin D analogs have been effectively used in the treatment of vitiligo, both as monotherapy and in combination with other modalities such as corticosteroids and UV therapy. Studies have indicated that the target of this therapeutic intervention lies in melanocytes and the immune system. Vitamin D, through its antiapoptotic effect, controls the activation, proliferation and migration of melanocytes by increasing melanogenesis and the tyrosinase content of cultured human melanocytes. Vitamin D also decreases the autoimmune damage of melanocytes by modulating T-cell activation.

Several clinical trials have been conducted to evaluate the role of topical vitamin D in vitiligo, in combination with other therapies [Table 4]. Since the existing clinical studies have shown variable efficacy of topical vitamin D, further studies are required to evaluate the exact relationship of serum vitamin D levels and vitiligo as well as to elucidate the effects of vitamin D in the treatment of vitiligo, either alone or in combination with other therapies. The role of oral vitamin D in the treatment of vitiligo has not been studied extensively. A pilot study was done to assess the efficacy and safety of prolonged high-dose vitamin D3 treatment of patients with psoriasis and vitiligo. This study was based on the fact that autoimmunity and vitamin D deficiency are related, and in turn vitamin D metabolism in affected patients is associated with the frequent presence of gene polymorphisms. Thus, giving high doses of vitamin D3 in patients with autoimmune disorders may compensate for inherited resistance to its biological effects. Finamor et al. treated 16 patients of vitiligo with 35,000 IU of vitamin D3 once daily for 6 months in association with a low-calcium diet and hydration. Fourteen of the 16 patients had 25–75% repigmentation with no significant change in metabolic parameters, thus indicating that high-dose
Vitamin D and skin disease

Table 3: Studies evaluating the role of vitamin D in atopic dermatitis

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hata et al.</td>
<td>14 patients, 4000 IU/day of vitamin D for 21 days</td>
<td>Increased cathelicidin expression in biopsied lesional skin</td>
</tr>
<tr>
<td>Sidbury et al.</td>
<td>Double-blind RCT, 1000 IU/day of vitamin D for 1 month during winter Supplementation: n=5; placebo: n=6</td>
<td>Significant clinical improvement in cases receiving supplementation, as compared to placebo</td>
</tr>
<tr>
<td>Samochcki et al.</td>
<td>95 patients with AD and 58 control subjects</td>
<td>Mean serum concentration of 25(OH)D3 in patients with AD was not statistically different from control subjects Frequency of bacterial skin infections was higher in patients with lower 25(OH)D3 levels No statistical associations were found between vitamin D levels and other multiple laboratory and clinical parameters After supplementation, both mean objective SCORAD and SCORAD index were significantly lower (P&lt;0.05)</td>
</tr>
<tr>
<td>Peroni et al.</td>
<td>37 patients</td>
<td>Found an inverse correlation between serum concentration of vitamin D and severity of the disease expressed by SCORAD index The prevalence of patients with sIgE to microbial antigens increased in relation to vitamin D deficiency and AD severity</td>
</tr>
<tr>
<td>Amestejani et al.</td>
<td>60 AD patients; randomized, double-blind, placebo-controlled trial First group: 1600 IU cholecalciferol (vitamin D); second group: placebo</td>
<td>SCORAD and TiS value index in the vitamin D group showed significant improvement in patients with mild, moderate, and severe AD (P&lt;0.05) as compared to placebo</td>
</tr>
</tbody>
</table>

Table 4: Studies evaluating the role of topical vitamin D in vitiligo in combination with other therapies

<table>
<thead>
<tr>
<th>Studies</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xing et al.</td>
<td>Calcipotriol 0.005%+betamethasone dipropionate 0.05% is an effective and well-tolerated therapy (response in 9/31 patients)</td>
</tr>
<tr>
<td>Rodríguez-Martín et al.</td>
<td>Tacalcitol ointment plus sunlight exposure has no added advantages over heliotherapy (RCT of 80 patients)</td>
</tr>
<tr>
<td>Birlea et al.</td>
<td>Vitamin D3 analogs are effective in combination with PUVA, NBUVB, or an excimer laser</td>
</tr>
<tr>
<td>Goldinger et al.</td>
<td>Addition of topical calcipotriol did not increase the efficacy of the 308-nm xenon chloride excimer (pilot study on 10 patients)</td>
</tr>
<tr>
<td>Oh et al.</td>
<td>Application of high concentration of tacalcitol with 308-nm xenon chloride excimer laser lowers the energy threshold significantly</td>
</tr>
</tbody>
</table>

vitamin D3 therapy may be effective and safe for vitiligo patients.

Vitamin D and ichthyosis

There are numerous reports of an association between disorders of keratinization and rickets in the literature. Calcitriol acts as an inhibitor of keratinocyte proliferation and also has a role in mineralization of new bones by increasing calcium and phosphorus absorption from the intestine. Thus, disorders like ichthyosis caused by abnormal keratinization may be associated with an alteration in vitamin D metabolism leading to rickets and osteomalacia. Though it still needs to be determined whether this association is causal or coincidental, it is suggested that children with severe ichthyosis living in developing countries and especially those with pigmented skin should undergo an evaluation for rickets.

The various factors leading to rickets in a patient with disorder of keratinization may include alterations in epidermal cholesterol metabolism, avoidance of sunlight to prevent sunburn, associated vitamin D deficiency rickets, or increased keratinocyte proliferation leading to poor penetration of skin by sunlight. Ingen-Housz-Oro et al. reported severe vitamin D deficiency [25(OH)D levels below 25 nmol/l] in nine patients with severe phenotypes of congenital ichthyosis (lamellar ichthyosis in four and the less severe congenital ichthyosiform erythroderma phenotype in five), most of whom did not improve after the sunny season. The deficiency was more severe and parathyroid hormone (PTH) levels were elevated in patients of North African descent who had pigmented skin, as compared to European patients. However, these patients had normal levels of markers of bone formation and resorption, and normal 1,25(OH)2D levels despite reduced 25(OH)D levels. The authors postulated that severity of deficiency in their cases may be related to the severity of ichthyosis and skin pigmentation. All but one patient improved after summer months and he also did not have normal 25(OH)D values typically found in healthy subjects with similar sun exposure.
Thus, it could not be definitely concluded whether the decreased vitamin D levels are a consequence of the keratinization disorder or are related to its physiopathology.

Sethuraman et al. described five children with ichthyosiform erythroderma who had biochemical and radiological features of rickets. Clinically three out of these five patients showed signs of rickets, with severe skeletal manifestations in two. Another study of 15 patients with keratinisation disorders showed increased serum PTH levels with low to normal 25(OH)D levels in 5 patients, possibly reflecting a secondary hyperparathyroidism due to subtle calcium or vitamin D deficiency. The findings may be a result of altered vitamin D metabolism due to disordered keratinisation, sun avoidance by patients, loss of calcium through skin or decreased calcium absorption due to retinoids ingestion. However, another study of 65 patients with keratinization disorders did not find any association between secondary hyperparathyroidism and vitamin D deficiency or retinoids intake.

Though studies have shown an association between vitamin D levels and keratinization disorders, its therapeutic role is still unclear as significant improvement has not been documented in ichthyosis despite restoration of biochemical values and healing of rickets after oral vitamin D supplementation in patients with coexistent pathologies. However, one patient showed improvement in ichthyosis following topical treatment. Thus, additional studies are needed to establish a cause-benefit relation of vitamin D and ichthyosis and to determine whether topical calcipotriene used in treatment of ichthyosis can also prevent vitamin D deficiency in them.

Vitamin D and skin cancer

The finding of vitamin D receptor expression on both normal and malignant cells initiated an investigation into the link between vitamin D and cancer. Ultraviolet radiation is a well known cause in the etiology of non melanoma cutaneous carcinomas. As previously mentioned, vitamin D offers protection to keratinocytes in vitro against UV radiation. Further, the development of cutaneous tumors in response to carcinogens in vitamin D receptor deficient mice has lead to the hypothesis that consistently raised serum vitamin D levels in response to chronic sun exposure protects against melanoma. Besides this, adequate serum vitamin D levels may decrease the incidence of solid organ tumors like those of stomach, liver, colorectum, gall bladder, pancreas, lung, breast, prostate, bladder and kidney, although the risk of non-melanoma cutaneous tumors is maintained due to the similar wavelengths required for vitamin D production and cutaneous photodamage. Studies have also revealed a correlation between serum vitamin D levels and cancer severity, with higher vitamin D levels observed in stage I melanoma vs stage IV tumor.

Promotion of cell differentiation and apoptosis along with inhibition of cancer cell proliferation, inflammation and angiogenesis by calcitriol
may explain the cancer protective benefits of vitamin D.\[79\] Hence, oral vitamin D supplementation can be recommended to significantly reduce the cancer mortality from melanoma and other solid tumors without increasing the risk of non-melanoma cutaneous cancers inherent to increased ultraviolet light exposure. However vitamin D receptor gene polymorphisms observed in various studies may lessen the benefit of vitamin D in some patients.\[80-82\]

**Vitamin D and skin fibrosis**

In a study by Zhang et al.,\[83\] the finding of inhibition of normal skin fibroblasts and keloid fibroblasts by vitamin D has suggested a potential therapeutic role in keloids. Topical vitamin D analogs are an established treatment modality in morphoea and lichen sclerosis et atrophicus owing to its effects on immunoregulation, fibroblast proliferation, collagen synthesis and endothelial cell function.\[84\] Suppression of T lymphocytes by calcipotriene leading to decreased IL-2 secretion may also explain its beneficial effect in morphoea.\[85,86\]

Application of calcipotriol ointment twice a day with overnight occlusion for 9 months was observed by Tay\[87\] to improve a plaque of morphoea in a 5-year-old child. Hulshof et al.,\[88\] reported improvement in joint mobility and skin extensibility in three patients of generalized morphoea after 3-7 months of treatment with 0.50–0.75 μg calcitriol oral daily without any untoward effects, which was maintained even after 1-2 years of discontinuation of therapy.

The basis for treating lichen sclerosus et atrophicus particularly extragenital disease, with vitamin D is similar to the rationale for its use in morphoea, although a precise mechanism of action has yet to be identified.\[89\]

**Vitamin D and infections**

Peacocke et al.,\[90\] reported a single case demonstrating an association of vitamin D deficiency with desquamative inflammatory vaginitis and resolution of the vaginal discharge when the circulating concentration of vitamin D returned to the normal reference range. Low vitamin D levels have also been associated with bacterial vaginosis.\[91\]

**Vitamin D and tuberculosis**

The long standing observation of improvement in tuberculosis on exposure to sunlight was not just coincidental. Induction of antimicrobial peptides, mainly cathelicidins by vitamin D may support its beneficial effect against *Mycobacterium tuberculosis*. A reduction in the population of viable bacilli has been demonstrated when infected macrophages are treated with dihydroxycholecalciferol.\[2\] Yuk et al. showed that LL-37, induced by physiological levels of vitamin D, stimulates access to and killing of *M. tuberculosis* even within autophagosomes.\[92\] This explains the occurrence of low serum vitamin D levels in patients with current or prior *M. tuberculosis* infection. Combined vitamin D and antitubercular therapy has been observed to result in a higher degree of clinical improvement than the latter given alone.\[2\]

The use of calciferol for treatment of lupus vulgaris dates back to 1940s. A series of cases from England, France, Belgium and other countries showed that calciferol had an excellent curative effect on lupus vulgaris without causing much toxicity.\[93\] Nnoham and Clarke\[94\] did a systematic review and meta-analysis to explore the association between low serum vitamin D and the risk of active tuberculosis in humans. From the seven observational studies published between 1980 and July 2006 and identified through Medline that were finally included in this systematic review, it was concluded that low serum vitamin D levels are associated with a higher risk of active tuberculosis.

**Vitamin D and autoimmune diseases**

There are various reports of vitamin D receptor polymorphisms associated with increased risk of various autoimmune disorders like Hashimoto’s thyroiditis, inflammatory bowel disease, Graves’ disease, rheumatoid arthritis, systemic lupus erythematosus (SLE), primary biliary cirrhosis (PBC), autoimmune hepatitis, Addison’s disease, vitiligo, celiac disease, type I diabetes mellitus and multiple sclerosis (MS).\[95\] However these reports mainly involve *in vitro* and animal studies, with only conflicting data in humans. In spite of this, vitamin D supplementation has been proposed for the therapy of autoimmune disorders.

**Other less-characterized roles of vitamin D**

Other less-characterized roles of vitamin D have been summarized in Table 5.
In view of the health benefits of vitamin D, multiple clinical and laboratory studies are underway to develop new vitamin D analogs with a better clinical profile. Some promising experimental compounds are: (1) analogs having predominant cutaneous metabolism thereby showing minimal systemic toxicity; vitamin D analogs, obtained by a combination of the 20-methyl modification with biologically interesting artificial side chain subunits or 2β-substituted calcitriols are promising candidates; (2) analogs with predominant cutaneous localization and without systemic side effects and (3) analogs with predominant effects on the target tissues and with minimal effects on calcium metabolism. This can be achieved by developing molecules showing variable affinities to vitamin D receptors and nuclear co-factors including retinoid X receptor α (RXRα).

**VITAMIN D IN THE INDIAN SCENARIO**

There is a false belief that vitamin D deficiency is uncommon in India. The data available in the published literature show vitamin D deficiency in all age groups and both sexes across the country. According to Harinarayan et al., factors like the solar zenith angle, time of day, season of the year, amount of ozone, cloud cover and latitude and altitude influence the amount of UVB radiation at a particular place, which in turn determines the amount of cutaneous in India. The serum concentration of 25(OH)D may be effected by variables like age, sex, pubertal status, latitude, season, race, and ethnicity.

Apart from low dietary intake causing vitamin D deficiency, people suffering from hepatic, renal and dermatological disorders, alcoholics and those suffering from inflammatory rheumatological conditions also have vitamin D deficiency. Other factors contributing to vitamin D deficiency in India are changing food fads and food habits, high-fiber diet, genetic factors (having increased 25(OH)D-24-hydroxylase which degrades 25(OH)D to inactive metabolites), more time spent indoors, increased pollution, cultural and traditional habits such as the use of “Burqa” in Muslims, and repeated and unplanned, un-spaced pregnancies in nutritionally deficient patients.

---

**Table 5: Other less-characterized roles of vitamin D in skin**

<table>
<thead>
<tr>
<th>Study</th>
<th>Dermatological disorder studied</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu'o'ng and Nguyen[96]</td>
<td>Seborrheic keratosis</td>
<td>Proteins linking vitamin D to SK pathology identified</td>
</tr>
<tr>
<td>Eciz et al.[97]</td>
<td>Rosacea</td>
<td>High vitamin D levels</td>
</tr>
<tr>
<td>Reichrath[98]</td>
<td>Aging</td>
<td>Both hypo- and hypervitaminosis D enhance aging. Normovitaminosis D seems to be important for preventing premature aging</td>
</tr>
<tr>
<td>Rasheed et al.[99]</td>
<td>Telogen effluvium and female pattern hair loss</td>
<td>Low serum ferritin and vitamin D levels observed</td>
</tr>
<tr>
<td>Burkiewicz et al.[100]</td>
<td>Leg ulcers</td>
<td>A trend toward better healing in those with vitamin D treatment has been noted</td>
</tr>
<tr>
<td>Agak et al.[101]</td>
<td>Acne vulgaris</td>
<td>Propionibacterium acnes induces an IL-17 response in acne vulgaris which is inhibited by vitamins A and D and, thus, vitamin D could be effective in treatment</td>
</tr>
<tr>
<td>Russell[102]</td>
<td>Xerosis</td>
<td>A correlation was observed between vitamin D levels and skin moisture content, with lower average moisture content in the skin of individuals with lower levels of vitamin D which improved significantly with topical vitamin D</td>
</tr>
<tr>
<td>Can et al.[103]</td>
<td>Behcet’s disease</td>
<td>Vitamin D improves the endothelial dysfunction</td>
</tr>
<tr>
<td>Marzano et al.[104]</td>
<td>Autoimmune bullous disorders</td>
<td>Low 25(OH)D levels may have a role in pathogenesis of these diseases and, in addition, may increase the risk of fractures in patients taking corticosteroids for treatment</td>
</tr>
<tr>
<td>Pal et al and Krul-Poel et al.[105,106]</td>
<td>Polycystic ovarian syndrome with acne and hirsutism</td>
<td>Potential therapeutic benefits of vitamin D in ameliorating the hormonal milieu and PCOS-related sequelae in women deficient in vitamin D have been reported</td>
</tr>
</tbody>
</table>

**Table 6: Role of vitamin D in skin disorders**

<table>
<thead>
<tr>
<th>Etiopathogenesis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-established role</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>Inconclusive</td>
<td>Atopic dermatitis, vitiligo, ichthyosis, keloids, autoimmune diseases</td>
</tr>
</tbody>
</table>

LSEA: Lichen simplex et atrophicus
vitamin D3 production. The Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) Expert Consultation[111] states that the abundant sunlight in most areas of the world between 42°N and 42°S latitude results in adequate cutaneous synthesis of vitamin D. Further, it proposes that thirty minutes of sun exposure over the arms and face in the absence of a sunscreen, preferably between 10 a.m. and 2 p.m. daily is adequate to avoid vitamin D deficiency.

Keeping in mind the enormous health benefits of vitamin D, guidelines for food fortification, vitamin D supplementation and adequate calcium intake for the Indian population should be formulated and implemented. As vitamin D insufficiency and deficiency are easily preventable, the current recommendations of taking 1–1.5 g of dietary calcium and 2000 IU of vitamin D per day in the diet should be adhered to avoid vitamin D deficiency.[110]

Table 6 summarizes the role of vitamin D in various skin disorders. Besides the role of vitamin D in the prevention of rickets and other bone disorders, interesting evidence has been unfolding on the relationship between vitamin D and other systemic diseases with many studies being undertaken to discover its other potential benefits though the data is still contradictory and insufficient for any clinical recommendations. Further studies are required to clarify the health promoting effects of vitamin D in humans.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

27. Ezquerra GM, Regana MS, Millet PU. Combination of acitretin...


33. van de Kerkhof P. Vitamin D and systemic therapy. Cutis 2002;70:1620.


81. Vitamin D and skin disease. Indian Journal of Dermatology, Venereology, and Leprology | July-August 2015 | Vol 81 | Issue 4