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Possible Role of Vitamin D in the Pathogenesis of Lichen Planus: Review Article

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ABSTRACT

Background: The skin, mucosa, and extremities can be affected by lichen planus (LP), a chronic lichenoid inflammatory condition. Rich inflammatory T cells infiltration, which travel in a band-like pattern in the upper section of the dermis, is a characteristic hallmark of LP. There have been numerous descriptions of the disease's various subtypes. Vitamin D regulates immunological function, making it a key factor in the development and progression of LP.

Objective: Review of possible role of vitamin D in the pathogenesis of Lichen Planus.

Methods: We scoured scholarly papers and databases including PubMed, Google Scholar, and Science Direct for information on Lichen Planus and vitamin D between May 1986 and January 2022, however only the latest or most comprehensive study was considered. The authors also assessed the usefulness of references taken from similar books. Documents written in languages other than English have been overlooked because of a lack of funding to translate them. Unpublished articles, oral talks, conference abstracts, and dissertations were all generally agreed upon to not constitute valid scientific investigation.

Conclusion: Vitamin D deficiency reduces Th2 cells and other T cells that are included among inflammation processes like T helper cells 11 and 17. This makes a bad situation much worse in inflammatory disorders like Lichen Planus.

Keywords: Vitamin D, Lichen Planus.

INTRODUCTION

A cutaneous condition known as lichen planus (LP) gets its name from the Greek word for "tree moss" (lichen) and the Latin word for "flat" (planus). Chronic inflammatory disorders of the stratified squamous epithelia are what we mean when we talk of LP. The latest understanding of LP is that it is an autoimmune illness mediated by T cells, when an interface dermatitis is brought on by the infiltration of cytotoxic CD8+ T lymphocytes. Possible causes of LP include exposure to viruses, pharmaceuticals, and contact allergies [(1)].

A recent review of 46 studies found that the prevalence of LP is 0.89%; among those who seek dermatological care. That number rises to 0.98%. Skin LP is uncommon compared to the more common oral form, with prevalence estimates ranging from 0.2% to 1.0% of the adult population. Less is known about LP's incidence, which varies widely from 14 to 250 cases per 100,000 people per year across different regions [(2)]. Rather than reflecting the existence of a racial bias, this variation likely reflects changes in sampling techniques between populations. In addition, patients with oral and cutaneous LP were combined in the aforementioned investigations, which used varying eligibility criteria. Unlike oral LP, which disproportionately affects women, cutaneous LP shows no clear sex bias [(3)].

Most cases of cutaneous LP appear between the ages of 30 and 60, and this age range accounts for about two-thirds of all cases. Oral LP typically manifests itself 10 years after its cutaneous counterpart does. There is no known racial or ethnic bias in LP, but a recent meta-analysis found a reduced overall prevalence of oral LP among individuals of Asian descent [(4)].

As things stand, our understanding of LP's epidemiology is patchy at best, gleaned from a few large-scale retrospective investigations and a few smaller ones. Due to the multidisciplinary nature of LP care in both primary and secondary settings, accurate estimates of its incidence and prevalence are difficult to obtain [(3)].

Idiopathic illness best describes lichen planus. While its exact cause is unknown, it appears to be a form of autoimmune disease mediated by T cells. The widely held belief is that epidermal self-antigens are changed and cytotoxic CD8+ T cells are activated in response to exposure to an exogenous substance such as virus and medication, or contact allergen. The mutated self-antigens trigger T-cell targeting and death by reacting with normal self-antigens on basal keratinocytes (Figure 1) [(5)].

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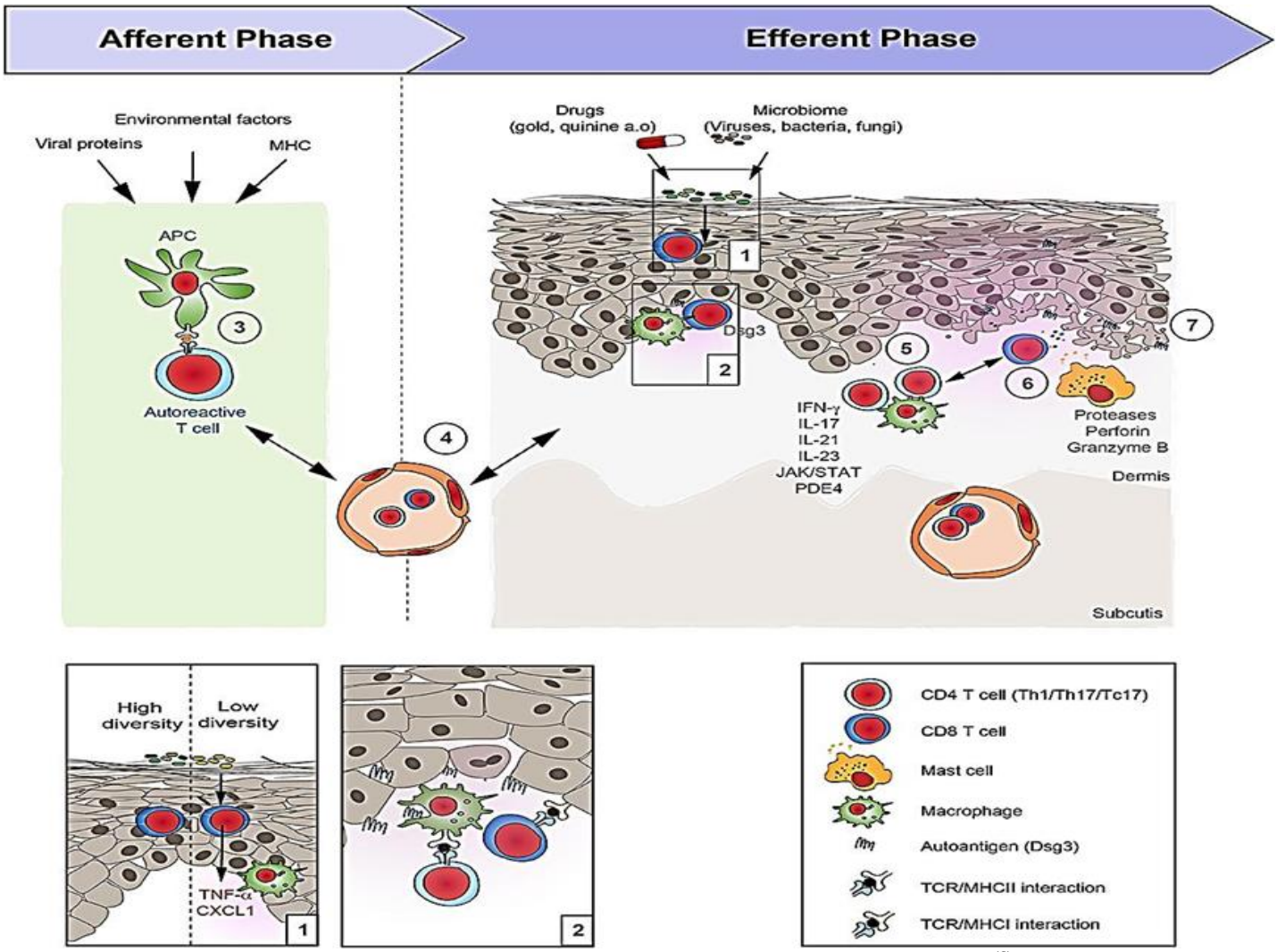

Figure (1): Pathogenesis of Lichen Planus exposed in a simple diagram [6].

Onset of lichen planus (LP) is typically gradual. Flexural surfaces of the limbs, including the wrists, are common sites for lesion development (Figure 2). After a week or more, a widespread eruption begins, with peak dissemination occurring between 2 and 16 weeks later [7].

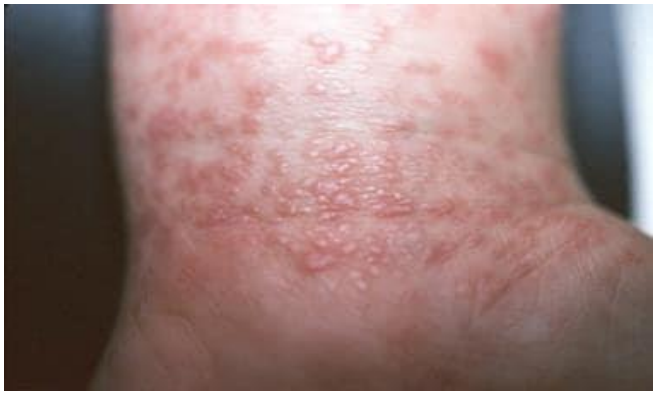

Figure (2): Lichen planus on wrist [7].

Calciferol refers to both Vitamin D3 as well as Vitamin D2. Vitamin D3 is either synthesized in the skin when UVB rays react with 7-dehydrocholesterol (7DHC) or taken orally. The majority of vitamin D2 comes from green plants. 25-hydroxylase in the liver converts 25-hydroxyvitamin D (25-OHD) or calcidiol from vitamin D3 and D2. Assays for vitamin D status typically focus on this form of the vitamin because it is the most abundant in the blood [8].

The body produces vitamin D, also called the "sunshine vitamin," in reaction to sun exposure, hence the name. Vitamin D aids in maintaining serum calcium levels in its normal amount and level, which is crucial for body health [9].

Vitamin D metabolism:

Because vitamin D dissolves in fat, it is absorbed into chylomicrons in the small intestine. Vitamin D-binding protein is responsible for transporting dietary vitamin D to the liver, where it remains bound to chylomicrons and lipoproteins [10].

25-hydroxyvitamin D2 and D3 (25OHD) linked to vitamin D-binding proteins are transported from the circulation to the kidneys. One binding site on this protein binds all vitamin D metabolites [11].

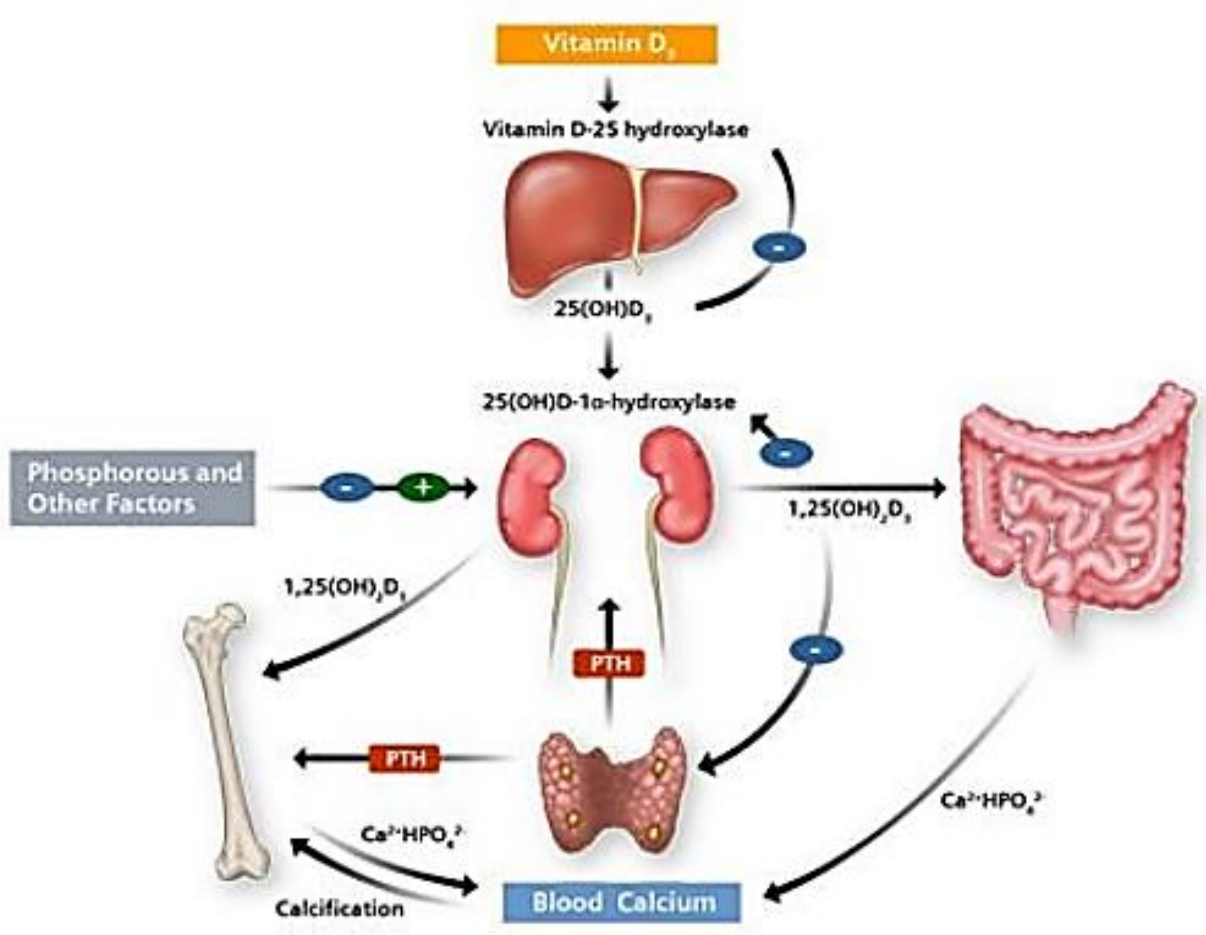

Figure (3): Vitamin D is involved in the regulation of calcium, phosphorus, and bone metabolism through its synthesis and metabolism [(12)].

Mechanism of Action:

The vitamin D receptor is a nuclear hormone receptor that is activated by 1,25-dihydroxyvitamin D. When vitamin D binds to its receptor, it alters gene transcription, turning on some genes while turning off others. As a result, the intestinal absorption of calcium as well as phosphorus is improved. Absorption of dietary calcium drops to about 10%-15% and phosphorus drops to about 60% without vitamin D. Vitamin D enhance calcium as well as phosphorus absorption by 30%–40% and by 80%, respectively, compared to when neither is present [(13)].

Sources of Vitamin D:

There aren't many food options that naturally contain vitamin D. Salmon, mackerel, and sardines are all examples of oily fish. Milk, orange juice (100 IU in an ounces serving), and certain breads as well as cereals are examples of vitamin D fortified foods [(14)].

Modifiers of UVB light reaching the skin have an effect on vitamin D making in the skin. Melanin in the skin soaks up UVB rays and blocks 7-dehydrocholesterol from being converted to vitamin D. Therefore, people with darker skin need more time in the sun to generate vitamin D because their skin produces less of it in response to UVB radiation [(15)].

In the winter, the sun's beams are more oblique, therefore more ultraviolet B (UVB) radiation is absorbed by the ozone layer. Consequently, skin exposure to harmful UVB rays is reduced. This explains why vitamin D production drops off throughout the winter. The amount of UVB sunlight that reaches the skin also decreases in latitudes higher than 37 degrees, leading to less vitamin D generation [(16)].

Vitamin D, being fat-soluble, is stored in the fatty tissues of the body. People who are overweight tend to store more vitamin D in their fat tissue. Therefore, to keep an adequate serum vitamin D level, people who are overweight need to take more vitamin D supplements [(17)].

Vitamin D poisoning almost seldom occurs. Exposure to sunlight does not cause vitamin D intoxication because the body excretes excess vitamin D in urine. Toxic levels of vitamin D can only be reached through chronic consumption of very large quantities. Hypercalcemia and vitamin D intoxication can occur at levels greater than 150 ng/mL (325 nmol/L). Constipation, polydipsia, polyuria, and

disorientation are all signs of vitamin D toxicity and hypercalcemia [18].

Vitamin D and immunity:

Vitamin D's role in controlling adaptive immunity is merely one of many possible physiological impacts. Adaptive immune responses often revolve around T and B cells. The genes that 1,25-dihydroxyvitamin D acts on in mature T helper (Th) cells to downregulate 57 and upregulate 45 have been determined. In addition to T and B lymphocytes, other key innate immune cells like neutrophils, macrophages, and dendritic cells also possess Vit. D receptors [19].

The adaptive immune response is affected by a wide variety of cell types. This compromised in suppressor cells, autoreactive T cells, as well as antigen processing cells. Dendritic cells (DCs) are type of immune cells which aid in shift of antigenic materials. DCs play a role in T cell stimulation through antigen presentation. Human DCs lose their surface marker expression capabilities in the presence of 1,25-dihydroxyvitamin D, including CD1a, MHC class II, CD40, CD80, and CD86. The vitamin D antagonist 1,25-dihydroxyvitamin D inhibits dendritic cell development at every stage [20].

Vitamin D and Skin Disease:

a. Psoriasis:

The potential for hypercalcemia rendered oral vitamin D ineffective as a therapy for psoriasis. Calcipotriol and tacalcitol, two topical vitamin D analogues, completely changed how this condition was treated once they were first developed. Psoriasis Area and Severity Index (PASI) scores are associated with serum 25(OH)D levels. Patients with low vitamin D levels also had higher PASI scores [21].

Patients with psoriasis with a body mass index of 27 or above had decreased 25(OH)D levels compared to those with a normal or low BMI. Psoriasis, as well as type 2 diabetes, obesity, and metabolic syndrome, have all been linked to vitamin D deficiency. Clinicians should recommend vitamin D-rich diets because of its beneficial effects on certain problems associated with psoriasis [22].

b. Atopic dermatitis:

Atopic dermatitis (AD) may be exacerbated by lack of vitamin D. It appears that the risk of AD in children increases with latitude. It is believed that the increased levels of Th2 cytokines like IL-4 and IL-13 found in AD patients hinder the proper induction of AMP. Patients with Alzheimer's disease may see an increase in cathelicidin levels after taking vitamin D orally [23]. **Hata *et al.*** [24] individuals with Alzheimer's disease and healthy controls were each given 4,000 IU of vitamin D3 daily by oral supplementation. The levels of cathelicidin in the AD patients increased by a factor of six. Norwegian youngsters with AD who were randomly assigned to spend four weeks in a subtropical climate showed improvement after returning home. Supplementing with vitamin D throughout the winter months may help people with AD, according to the results of a small pilot trial. It appears that vitamin D supplementation would be helpful in the treatment of AD, however this must be confirmed in larger research [25].

c. Vitiligo:

Fifty vitiligo patients had lower serum vitamin D levels than healthy controls, and this difference inversely correlated with disease severity [26]. As per a meta-analysis, low levels of vitamin D are associated with vitiligo. Vitamin D analogues have shown mixed outcomes whether used alone or in combination with other therapies to cure vitiligo. However, there are no randomised controlled trials showing that vitamin D supplements are helpful for these patients [27]. Overall, vitiligo patients and healthy controls did not differ significantly in vitamin D levels. However, subgroup analysis revealed that vitiligo patients who were male, younger, had vitiligo for a shorter duration, and had not received phototherapy had the lowest vitamin D levels [28].

The pathogenesis of vitamin D among lichen planus patients:

Vitamin D regulates immunological activity, making it a key player in the development and progression of LP. However, Vitamin D3 is the active form of the vitamin, and it has been linked to a wide variety of malignancies and autoimmune illnesses, as well as having a hand in controlling the expression of numerous crucial body genes. Fewer Th2 cells and more pro-inflammatory Th1 and Th17 cells are the result of insufficient vitamin D. This exacerbates the harm caused by inflammatory diseases like LP. Vitamin D levels should be monitored in the general population, especially in those who have LP [29].

Severely low vitamin D levels were observed in lichen planus patients [30]. When vitamin D levels are insufficient, there are fewer Th2 cells and more Th1 cells and Th17 cells, which are also implicated in inflammatory pathways. Diseases with inflammation, such as lichen planus, are exacerbated by this [29].

Patients with lichen planus were studied to determine if topical calcipotriol was useful in treating the condition. Due to the fact that 56.3% of patients showed improvement while 43.8% did not. Researchers found that calcipotriol wasn't perfect, but it showed promise as a potential treatment for lichen planus. In a different trial, the effectiveness of calcitriol and betamethasone valerate in the treatment of lichen planus was examined. Lesion thickness, pigmentation, and pruritus did not differ significantly across groups after 12 weeks of usage. Systemic corticosteroids as well as

narrow band were compared as potential treatment options for lichen planus. Narrow-band UVB three times weekly outperformed prednisolone 0.3 mg/kg after 6 weeks of treatment for systemic lichen planus [(31)].

In a separate study, researchers looked into how exposure to narrowband UVB light affected participants' vitamin D levels. Patients who were given oral D3 supplementation at a dose of 400 international units per day had significantly lower levels of vitamin D than those who were treated with whole-body narrow-band UVB at the lowest erythema dosage three times per week. Cases who had light eruptions, atopic dermatitis, vitiligo as well as atopic dermatitis showed high vitamin D levels beyond getting treated by narrow band UVB [(32)].

This relationship between low plasma levels of vitamin D and serum vitamin D levels was first uncovered in a case report that was conducted in India by **Varma *et al.*** [(33)]. Three individuals diagnosed with ocular lymphoma phlebitis and one patient diagnosed with both ocular and cutaneous lymphoma had low vitamin D levels. It is difficult to attribute the improvement in the patient's mucosal lesions and lack of paresthesia while on oral vitamin D supplementation to the vitamin alone because the patient was also being treated for LP. [(33)].

Vitamin D's effectiveness in warding off oral lichen planus has been the subject of a plethora of research (OLP). Vitamin D insufficiency may contribute to the aetiology of OLP, since it has been demonstrated in studies to suppress epithelial production of interferon gamma (IFN-) and interleukin 1 beta (IL-1). Results from epidemiological research were inconsistent when examining the involvement of vitamin D and its receptors in the aetiology of osteoporosis-related bone pain (OLP). Although there was no significant difference between the two groups in prior research, this one found that persons with OLP had considerably lower serum levels of vitamin D compared to healthy controls [(34)].

CONCLUSION

Vitamin D deficiency reduces Th2 cells and other T cells that are included among inflammation processes like T helper cells 11 and 17. This makes a bad situation much worse in inflammatory disorders like Lichen Planus.

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Competing interests:

Nil.

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