



BENEFICIAL EFFECTS OF VITAMIN D AND ITS ANALOGUES IN THE PHARMACOTHERAPY OF PSORIASIS “An Analytical Review”

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ABSTRACT Vitamin D is an important fat-soluble vitamin with multipronged pleiotropic effects that is being studied at large in the recent past. The novel discovery of its systemic role in modulating the immune mechanism coupled with its anti-inflammatory activity has triggered a lot of research to decipher its effect in the treatment of various inflammatory conditions ranging from psoriasis, multiple sclerosis, obesity, diabetes mellitus, depression, chronic fatigue and metabolic syndrome. In the recent past, with a view to decipher the exact pathogenetic mechanisms of Psoriasis, it was widely studied and the fact that this is a systemic disease centered on inflammation from various pathways more so through the Th1 pathway came to limelight. There is high degree of association between psoriasis and low vitamin D levels. Basic research to understand the cutaneous defences has highlighted the fact that vitamin D play an important role in downregulating the hyperproliferation of keratinocytes that is implicated in the pathogenesis of Psoriasis, Vitamin D strengthens the cellular junction in the cells of the skin and prevents the infiltration of macrophages thus preventing widespread inflammation. Genetic polymorphism in Vitamin D Receptor (VDR) is implicated in increased pre-ponderance of person developing Psoriasis. Vitamin D preparations in its topical form have demonstrated excellent efficacy in many meta-analyses in the recent times as a monotherapy or in combination with a topical steroid added up with lesser degree of cutaneous toxicity on prolonged use. Hence through this review we aim to analyse and highlight the beneficial role of vitamin D in the treatment of psoriasis which can pave a path for carrying out extensive research in the form of Randomised clinical trials which could help to develop systematic reviews and meta-analysis for formulating an evidence-based approach for incorporating the role of vitamin D in the treatment of Psoriasis.

Psoriasis has been recently established to be a systemic disease revolving around inflammation and involvement of cytokines of the Th1 pathway. There is an increased prevalence of metabolic syndrome in patients with psoriasis. Metabolic syndrome also involves a proinflammatory state. This paper proposes the idea of the potential use of oral vitamin D to treat psoriasis and metabolic syndrome concurrently. We propose there is merit in more clinical trials investigating the use of vitamin D to treat both psoriasis and metabolic syndrome through its anti-inflammatory effects. On application to psoriasis management and prognosis, the goal is to decrease the risk for cardiovascular disease and decrease disease morbidity and mortality.

KEYWORDS : Vitamin D; Psoriasis; Pleiotropic Effects; Topical Vitamin D; Vitamin D Receptor

INTRODUCTION

Vitamin D receptors are ubiquitous, many studies in the recent past have concluded that vitamin D receptors are present in most of the tissues and cells of humans, this has led to a wide sprung interest to decipher the role of vitamin D in various pathophysiological conditions in human health and diseases. It is studied to a larger extent that vitamin D exhibits multipronged pleiotropic effects in various disease conditions like carcinomas of the breast, prostate and colorectal malignancies to its beneficial role in cardiovascular, metabolic, endocrine, autoimmune and other chronic inflammatory pathologies.^[1]

It is interesting to note that many studies in the recent past have demonstrated the role of vitamin D on cellular proliferation, differentiation, angiogenesis and apoptosis which is being harnessed in many ongoing trials to look into the benefits of vitamin D supplementation in conditions involving these pathogenetic mechanism. In many studies vitamin D has demonstrated efficacy as an immune regulatory hormone with its additional benefit of possessing anti-inflammatory properties which is mediated by helper T

cells (Th1) and this property is found to possess beneficial effect in chronic inflammatory conditions like Multiple Sclerosis, diabetes, psoriasis, psoriatic arthritis etc.^[2] Psoriasis is a chronic and common inflammatory disease that is characterized by presence of chronic inflammatory cells like the Th1 cells and is clinically characterised by the presence of scaly skin plaques, that can often be painful and itchy and is usually associated with chronic formation pus and pruritis due to the occurrence of secondary infections.^[3] In many instances, Psoriasis is associated with co-morbid conditions like diabetes mellitus, arthritis of psoriatic origin, metabolic syndrome, depression, cancer and presence of chronic fatigue.^[4] Extensive research carried out in the past shows that vitamin D is beneficial in the improvement of clinical conditions associated with depression, obesity, diabetes mellitus and chronic fatigue, such alleviation of clinical symptomatology points that this vitamin exerts multipronged Pleiotropic effects could prove beneficial in the treatment of Psoriasis.^[4,5]

The primary manifestation of Psoriasis is usually found in the cutaneous surface with a rate of prevalence ranging from 2% to 3% in

the general public. Inflammatory reactions can also occur in other organs of the body, hence attributing systemic manifestation to the primary form of this chronic disease and it often co-exists with other conditions like metabolic abnormalities which can range from diabetes, central obesity and psoriatic arthritis.^[6] All these conditions predispose a patient to develop severe cardiovascular symptoms, hence this condition has to be dealt with utmost clinical suspicion and treated appropriately.

In its full-fledged form, this dermatosis is characterised by the presence of keratinocytes that is hyper-proliferation, impaired epidermal barrier functions at the site of skin lesion, which increases the preponderance of inflammatory cells that seep inside the skin layer and result in chronic inflammation.^[7] It is challenging to treat this condition that the exact pathogenesis is not clearly evident till date, but largely the pathogenesis is attributed to the factors that regulates the development of auto-immune, hormonal, genetic and other psychological causes with somatisation, it is necessary to harness the beneficial effects of vitamin D that can contribute to a large extent in the prognosis of Psoriasis alone or as an additional supplement with other anti-psoriatic medications.^[7,8]

BRIEF FACTS ABOUT VITAMIN D

Vitamin D, which is also referred to as "Calciferol" or the sunshine vitamin, belongs to the fat-soluble category of vitamins that is naturally present in certain food items and in few other they are fortified and is also available as a supplement for therapy.^[9] It is produced endogenously when ultraviolet rays (UV) rays from sunlight gets incident on the skin "the concept of zenith angle", which then triggers the synthesis of vitamin D in the body. The activation of vitamin D that is obtained by various sources has to undergo two hydroxylation reactions in the body for its activation and subsequent action.^[10] The first hydroxylation that occurs in the liver converts vitamin D to 25-hydroxy vitamin D which is popularly called as Calcidiol. The second hydroxylation occurs in the kidneys which converts Calcidiol to its physiologically active form called as Calcitriol or 1,25 Di-hydroxy cholecalciferol.^[11]

Vitamin D promotes the absorption of calcium in the gut and hence maintains the normal phosphate concentrations to enable normal mineralization of bone and prevents hypocalcaemia related tetany, it is also necessary for normal growth of bones and mineralisation without which an individual is at risk of fractures due to osteoporosis attributed to deficiency of vitamin D related deficient calcium levels in the blood.^[12] The effective role of vitamin D in the treatment of Psoriasis as an supplement therapy is debatable and controversial, through this review we aim to clearly outline the multifunctional role of vitamin D in the treatment of various inflammatory pathologies which also includes Psoriasis.^[13]

AN OVERVIEW OF PSORIASIS

When initially Psoriasis was extensively explored it was noted that it primarily affects the keratinocytes of the epidermis and its proliferation which results secondary to cutaneous inflammatory infiltration. Last decade has seen tremendous research in decipherment of pathogenesis of Psoriasis.^[14] It is now evident that Psoriasis is a systemic inflammatory disease that is mediated through the immune system of our body, which primarily involves the helper Th1 cells.^[15] It is now a well-accepted fact that an unknown stimulus activates the cutaneous antigen presenting cells, these cells activate the T helper cells which leads to subsequent release of a cascade of inflammatory cytokines. This cascade recruits the other cell types like the neutrophils, chemokines, growth factors and other endothelial cells. All these events result in the hyperproliferation of keratinocytes, which eventually presents as a psoriatic lesion of the skin and its subsequent sequelae.^[16] Very recently, Interleukin-17-secreting helper T cells have been contented for its implication in inducing the expression of chemo-attractants that are found in psoriatic lesions. These Th17 cells are also studied to secrete interleukin 22, which is involved in the excess proliferation of keratinocytes.^[17]

EFFECTS OF VITAMIN D ON SKIN BIOLOGY

The complex mechanism of vitamin D as a regulator of skin physiology is yet to be known as such, it is well known that the stem cells within the basal layers of the skin continuously divide throughout their life span and progress to move upwards to stratify and form a barrier mechanism of the skin, it is important to note that the differentiation of the epidermis is a complex process which occurs in sequence and is under tight control, the precursor of vitamin D is

located in the keratinocytes of the basal spinous layer of the skin. Post activation to calcitriol that binds to its receptors and controls the differentiation and proliferation keratinocytes, the barrier system of the skin, the immune mechanism of protection of skin and the process of apoptosis.^[18]

Numerous studies in the recent past have shown a dose dependent proliferation of keratinocytes both *in vivo* and *invitro*, whereas at higher doses pharmacologically an inhibitory effect became apparent. It is also seen that the levels of S100A7 in psoriatic skin is more in contrast to normal skin and this upregulation is inhibited by the analogues of vitamin D which is seen in reconstituted human skin.^[19] It is also studied that vitamin D plays an important role in cellular proliferation in the zone of stratum Basale and also increases the synthesis of keratins (K1 and K10), involucrins, transglutaminases, filaggrins and loricin. Hence the capacity of vitamin D to regulate the intracellular levels of calcium is well documented in these studies, it is also documented that the levels of vitamin D is less in conditions involving disruption of epidermis, which reduce the levels of involucrins and loricin and loss of keratinohyalin granules that result in hyperproliferation of keratinocytes and the pathognomonic signs of plaques and lesions of Psoriasis.^[20]

ROLE OF VITAMIN D IN REGULATION OF CUTANEOUS IMMUNITY

Vitamin D plays an important role as an immunomodulator that is pluripotent which inhibits the proliferation of T lymphocytes and induces the generation of CD4+ Tregs/CD25 (Cluster of Differentiation), a phenotype of T cells that promotes the tolerance and inhibits immunity after sensitization with the antigen. Vitamin D also induces the expression of a chemokine receptor (C-C Chemokine) that is involved in the T cell mediated inflammation of skin and their migration from the blood vessels of tissues of dermis to epidermis and its keratinocytes.

Vitamin D, by the virtue of its immune modulating property helps to defend our body from opportunistic infections by induction of autophagy in macrophages of humans.^[21] It also supports the innate skin barriers against invading bacteria, fungi and viruses in conjunction with the cathelicidins and defensins (Antimicrobial Peptides) that are synthesised as a result of vitamin D mediated induction of defence mechanisms of the cutaneous tissues. These Antimicrobial peptides also plays an important role in the release of cytokine, chemokine release, antigen presenting cell proliferation, increasing vascular permeability, wound healing and angiogenesis.^[22]

THE ASSOCIATION OF VITAMIN D AND PSORIASIS

Extensive studies are carried out in the recent past including ongoing trials that points out the role of vitamin D in the maintenance of the cutaneous barrier mechanism and its homeostasis, vitamin D receptor polymorphism and psoriasis susceptibility is also been identified, a recent study conducted by Junlin lui *et al.*,^[23] has observed the association of psoriasis and vitamin D receptor polymorphism wherein it stated that the VDR gene polymorphisms are associated with susceptibility to psoriasis. A total of 110 patients and 183 controls were genotyped for VDR gene polymorphisms rs2228570, rs731236, rs1544410 and rs7975232 by LDR method. SNP-based and haplotype-based association analyses were subsequently performed. Patients with PASI < 3 were treated with calcipotriol ointment monotherapy. After 6 weeks of therapy, the correlations between efficacy and the genotypes of each polymorphism were evaluated.^[23] The results showed that for rs7975232, allele A was significantly over-represented in psoriasis patients relative to controls, which clearly states the association of VDR polymorphism and preponderance to develop Psoriasis. It is also noteworthy to observe that the tight junctions are fundamental to increase the barrier mechanism by regulating the adhesion and permeability of keratinocytes and also to promote the cutaneous cellular defence, many studies have pointed out vitamin D as a key modulator of inflammation.^[24] Calcitriol is studied to exert anti-inflammatory effect by the process of downregulating the expression and production of several pro-inflammatory cytokines and chemokines including IL-1 β , TNF- α , IL-6 and IL-8.

There is an increasing school of evidence that shows a close correlation between low vitamin D among patients of Psoriasis than the normal cohorts after adjusting for the confounders. Few studies conducted in the recent past also elaborates the role of vitamin D in psoriatic arthritis and attributes an inverse relationship with disease pathology.^[25]

TOPICAL FORMULATIONS OF VITAMIN D AND ITS IMPLICATIONS IN THE TREATMENT OF PSORIASIS

It is a well known fact that is known to the world since the dawn of extensive research in vitamin D and its pleiotropic effects since 1985 which is confirmed from a large number of trials.^[26] The derivatives of vitamin D are calcitriol, calcipotriol, tacalcitol, maxacalcitol and hexafluoro-1,25(OH)₂D these are confirmed for their efficacy in psoriasis in numerous clinical trials.^[27] Vitamin D therapy in its topical form is the most popularly prescribed medication for this disease as the first-line, singly or in combination with other anti-psoriatic medications that included topical steroid preparations.^[28] The efficacy of topical calcipotriol is also documented in various studies involving localised plaque psoriasis.^[29] The beneficial effects of topical vitamin D preparations are highlighted in many studies where they concluded that difficult to treat areas in Psoriasis like the face and inguinal atrophy can benefit at large with topical preparations of Vitamin D and without any evident toxicities. It is important to note that topical preparations of vitamin D have no major drug reactions that is noted in any study done till now, a few meta-analysis have demonstrated and documented the fact that the topical vitamin D preparations when used as monotherapy was equally efficacious to topical steroid viz a viz., superior efficacy when used in potent combination of a topically potent steroid formulation.^[30] The steroid sparing effect of vitamin D, needs further research as it can be a potent breakthrough in treating a lot of pathologies where immune mediated mechanisms have been implicated in the development of severity of these intrusive conditions.

CONCLUSION

Vitamin D being an important vitamin that exhibits a variety of pleiotropic effects and with its profound effect in the proliferation and differentiation of keratinocytes in conjunction with its immune modulatory and inflammatory suppressive actions have attracted wide interest in its role in the treatment of psoriasis either as a monotherapy or in combination with other anti-psoriatic medications.

A variety of studies that have been done in the past shows a clear association between low levels of vitamin D and preponderance in developing Psoriasis, Although the exact mechanisms of the role of vitamin D in the pathogenesis and treatment of Psoriasis is unclear, but extensive basic research points out to its interaction with the vitamin D receptors in the basal layers of the skin and regulation of calcium associated with suppression of proliferation of keratinocytes that is the key in the development of characteristic lesions of Psoriasis.

Pleiotropic effects of vitamin D in various conditions like cancers of the breast, colon, prostate and testis and other autoimmune diseases like SLE, Multiple Sclerosis, Psoriatic Arthritis, Diabetes Mellitus, Obesity and Metabolic malfunction is proved to a larger extent.

Hence this information will pave a path for the clinicians to understand and decipher the benefits of vitamin D preparations in their routine practice, so the healthcare industry could benefit from the multipronged effects of this vitamin that is abundantly available but yet the deficiency predominates leading to the nidus of various pathological conditions.

LIMITATIONS

This is a limited review to delineate the benefits of vitamin D in Psoriasis, extensive research and systematic reviews including a huge number of RCTs done in the past has to be incorporated to generalize the observation and improve the class evidence.

FUTURE DIRECTIONS

Through this study the researchers look forward to carry out elaborate and extensive research that includes systematic reviews and meta-analysis.

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