

expression and perpetuation of lesions, are found activated and in greater number in the papillary dermis [12]. Antioxidant properties of vitamin A and its derivatives have also been implicated in its efficacy on psoriatic plaques [13,14].

Tazarotene, a topical form of retinoid, exhibits efficacy in the treatment of plaque psoriasis and has been shown to be non-inferior to steroid creams in palmoplantar psoriasis [15,16]. Acitretin has been used as monotherapy and in combination therapy for various types of psoriasis. In a study using escalating doses of acitretin alone in severe chronic plaque psoriasis, greater than 50% of patients achieved a 54-76% reduction in Psoriasis Area Severity Index (PASI) score in twelve weeks with 35-50mg/day dosing [17]. Although monotherapy is effective, it is often more effective and can be used safely in combination with other therapies, particularly UVB therapy [18,19].

Several studies have shown a vitamin A deficiency in patients with psoriasis. In a sizeable study with adjustments for age, race, gender, vitamin intake, smoking status and BMI, the provitamin for vitamin A, carotenoid was found to be decreased in the skin of psoriasis patients compared to those without disease [20]. A study by Majewski et al. looked at the systemic levels of vitamin A and found a decrease in all psoriasis patients compared to controls. Additionally, the study found the levels correlated with disease activity—levels were lower in more active disease [21]. Further studies are needed to clarify the relationship between vitamin A levels and supplementation in the management of psoriasis.

Vitamin D

The efficacy of vitamin D in psoriasis is based upon its inhibition of keratinocyte proliferation due to genome mediated effects and induction of keratinocyte differentiation by increasing intracellular calcium levels [22,23]. Vitamin D also exerts anti-inflammatory effects inhibiting the production of numerous inflammatory cytokines through the direct inhibition of T cells and T regulatory cell induction. More specifically, vitamin D has been found to downregulate toll-like receptor (TLR) expression, key initiators of the inflammatory cascade and cellular proteins implicated in the pathogenesis of psoriasis [24]. One study showed an increase in TLR2 induced production of cytokines in vitamin D deficient patients with levels <50 nmol/L. After normalization to >100 nmol/L through supplementation, TLR2-dependent production of cytokines was significantly reduced [25].

The physiologic mechanism by which TLRs exert their inflammatory activity is through detection of pathogen-associated molecular patterns. After activation, TLRs initiate a signaling cascade which terminates with increased activity of nuclear factor kappa-B (NF- κ B) among other proteins. NF- κ B is a major protein responsible for signaling production of tumor necrosis factor- α (TNF- α) and other pro-inflammatory interleukins [26]. Specifically, TLR2 and TLR4 have been shown to play a significant role in psoriasis and other cutaneous disease processes [26-30]. In a study investigating the expression of TLRs in cutaneous disease, TLR2 and TLR4 were shown to be disproportionately expressed in psoriasis affected epidermis [27]. The identification of augmented expression of TLRs in and their contribution to psoriasis is supported by numerous studies showing the role of various receptors in psoriasis including increased epidermal TLR2 expression [28-29]. Another study showed that TLR2 and TLR4 polymorphisms were found to increase patient susceptibility to psoriasis vulgaris [30]. Allen et. al. showed a high density of TLR2 within upper dermal capillaries within psoriatic plaques supporting a systemic innate immune response [31].

Topical vitamin D analogues are mainstays of therapy following steroid or vitamin A therapy failure in psoriasis. Various studies determined both calcitriol and calcipotriol were just as effective as betamethasone dipropionate and were also effective as stand-alone therapy. Combination therapy with topical steroids has a synergistic effect and is commonly used in practice. The short-term adverse effect of topical vitamin D is minimal if present and consists of only minor facial dermatitis. Calcium level alterations were not seen in any studies [32-34]. Long-term safety and efficacy studies have also demonstrated efficacy and an excellent safety profile for topical tacalcitol [35-37].

While topical forms of vitamin D have proven effective, oral vitamin D supplementation should be considered in cases with significant body surface area involvement. A variety of studies have shown that oral vitamin D supplementation and vitamin D analogues have favorable clinical responses and maintain a similar safety profile to topical forms. Although patients did not experience adverse outcomes, the risk of hypercalcemia and bone demineralization is theoretically possible [38-41]. With the literature support for oral vitamin D, the next step is producing a vitamin D analog that can target the underlying pathophysiology of psoriatic lesions while minimizing adverse effects. Although the topical vitamin D analogues are effective, each has its disadvantages when administered orally, making a synthetic vitamin D alternative an ideal possibility [42,43].

Several studies have provided evidence to support vitamin D deficiency in psoriasis. In a cross-sectional study, vitamin D levels were measured over the course of one year in psoriasis, rheumatoid arthritis (RA), and healthy control patients. Not only did >50% of psoriasis patients have vitamin D deficiency, the percentage rose to >80% in the winter months while both RA patients and healthy controls showed deficiency in less than half [44]. An additional study identified vitamin D deficiency in 68% of patients with chronic plaque psoriasis, while 97% were insufficient. The same study also determined vitamin D levels correlate with disease severity [45]. A more recent case report showed a novel presentation of deficiency and subsequent improvement with supplementation as psoriasis developed after TNF- α administration for RA. The patient underwent vitamin D testing for a personal history of osteoporosis. Upon identifying a deficiency, supplementation was initiated resulting in lesion resolution [46]. While vitamin deficiency is supported in the literature, an older study found that affected fibroblasts within psoriatic lesions are moderately resistant to activated forms of vitamin D *in vitro* [47]. This finding may support the efficacy of topical vitamin D administered at greater concentrations than that found in endogenous vitamin D. The study could also represent a mechanism for functional deficiency in patients with otherwise normal vitamin D levels.

Vitamin E

Vitamin E is a major cutaneous, non-enzymatic antioxidant, scavenging free radicals generated through a variety of mechanisms leading to skin pathology. Vitamin E is also anti-inflammatory as demonstrated in numerous animal models [48]. Only two forms of vitamin E exist in the body: α -tocopherol and γ -tocopherol. Both occur in abundance within the stratum corneum after their secretion by sebaceous glands [49-51]. The increased density of vitamin E within the stratum corneum preserves the integrity and barrier function of the skin while protecting the most superficial cutaneous layer from oxidation [52]. Supplementation of vitamin E, orally or intravenously, has been shown to reach the outermost portions of the skin and does so within two weeks of supplementation [53].

The current standard for psoriatic therapy does not capitalize on the proposed protective mechanisms of vitamin E, but several studies have shown vitamin E efficacy in psoriasis. An animal study showing the topical application of methanolic extract of *Andrographis nallamalayana* on psoriatic lesions showed alleviation of symptoms within 12 days. The extract contains α -tocopherol among other natural chemicals [54]. A case report detailed the efficacy of nutritional supplementation and diet manipulation without concomitant standard psoriasis treatment in a 36-year old female with psoriasis. The diet eliminated all processed foods and sugars; the nutritional supplementation contained 29.1 mg of α -tocopherol, 2.6 mg of additional natural tocopherols and >35 additional vitamins, minerals and amino acids. The patient experienced complete disease remission by six months [55]. A more formal study identified fifty-eight hospitalized patients with psoriasis and supplemented half of patients with coenzyme Q10, vitamin E and selenium. They measured markers of oxidative stress within the epidermis and monitored clinical outcomes. Supplementation proved effective for both improvement in cutaneous oxidative stress and clinical disease [56]. These studies all support the role for vitamin supplementation in psoriasis management, but the addition of various other compounds confounds the role of vitamin E specifically.

One major form of incidental vitamin E supplementation in the diet is through olive oil. Numerous studies have determined a high content of tocopherols in olive oils through various methods of extraction [57-59]. Dietary olive oil supplementation in mouse models has provided promising anti-inflammatory results. One model fed mice extra virgin olive oil (EVOO) prior to arthritis induction with type II collagen. The EVOO-fed group prevented arthritis development through a significant reduction in inflammatory cascades, notably the Janus kinase/signal transducer and activator of transcription (JAK/STAT), mitogen-activated protein kinase (MAPK), and NF- κ B pathways, resulting in a reduction of pro-inflammatory activity [60]. Another mouse model found a dramatic reduction in renal and splenic expression of the same inflammatory cascades, JAK/STAT, MAPK, and NF- κ B, with an EVOO diet in mice with pristane-induced systemic lupus erythematosus. Furthermore, antioxidant effects of EVOO were found via up-regulation of heme oxygenase 1 (HO-1) and nuclear factor E2-related factor 2 (Nrf-2) proteins in the EVOO group [61]. A recent study conducted by Praticó demonstrated the prominent disease-modifying properties of EVOO in Alzheimer's disease (AD). Transgenic mice were supplemented with EVOO; investigators found a significant decrease in amyloid- β peptide and phosphorylated tau protein, synaptic integrity was maintained and behavioral deficits were ameliorated with EVOO supplementation [62]. These studies support the immunomodulating role of olive oil through oral supplementation, providing support to a role for vitamin E in modulating inflammatory pathology.

Few studies exist determining vitamin E levels in psoriasis patients. A recent study found a decrease in intraepidermal levels of vitamin E, coenzyme Q10, and selenium in both psoriasis and atopic dermatitis [63]. While this may support a potential overall deficiency, systemic vitamin E deficiency in psoriasis has yet to be shown in the literature. Due to the uncommon practice of vitamin E testing and rare finding of deficiency in the general population, testing vitamin E levels is rare. Further research is indicated to determine if deficiency exists in psoriasis.

Vitamin K

Vitamin K is classified into three types: K1, K2, and K3. K1 is responsible for the production of coagulation factors and plays a role in vessel calcification homeostasis. K3, menadione, prevents deficiency as an enzyme cofactor. K2, menaquinone, impacts bone health, alters calcification in the cardiovascular system and limits inflammation among its other effects in various tissues making it a target for research in autoimmunity [64].

Vitamin K decreases inflammation through a variety of pathways. Several *in vitro* studies showed vitamin K2 inhibits production of prostaglandins and major pro-inflammatory cytokines including IL-1, IL-6, TNF- α [65-68]. While one study identified the prevention of oligodendrocyte production of 12-lipoxygenase with vitamin K2 addition, the remaining studies focused on the effects of vitamin K2 addition to both macrophages and fibroblasts. *In vivo* studies also suggest vitamin K has a role in lowering concentrations of inflammatory markers in several organ systems. The Framingham Offspring Study gave rise to the inverse relationship between vitamins D and K and inflammatory markers with exogenous supplementation. The study measured 14 different inflammatory markers and found significant reductions in 5 markers with vitamin K supplementation. The remaining 9 markers exhibited a decrease with supplementation albeit less significant [69].

Specific research on the positive effects of vitamin K in autoimmunity exists in the literature. A clinical study on the effects of vitamin K2 supplementation in the treatment of RA used 100 μ g/day of menaquinone-7 for three months without changing the established medication regime of RA patients. At the end of the study, the vitamin K2 supplemented group showed a significant decrease in erythrocyte sedimentation rate, C-reactive protein (CRP), matrix metalloproteinase (MMP-3), and clinical disease score among other markers [70]. An additional study with 45mg/day of vitamin K2 supplementation in RA patients showed a decrease in serum CRP and MMP-3. Each of these studies supports the systemic anti-inflammatory effects of vitamin K supplementation [71].

A defined mechanism to support the clinical effects of vitamin K has been recently purported through TLRs. The study used vitamin K supplementation in mice to detect its effect on vascular calcification and direct effect on inflammation within the vessel. After 12 weeks of 40mg/kg/day of oral vitamin K, aortic tissue showed a significant decrease in TLR2 and TLR4 expression as measured by immunohistochemistry [72]. The recent study exhibiting vitamin K associated downregulation of TLR2 and TLR4 is an important discovery as psoriasis has aberrant expression of such receptors in the epidermis as previously stated. The efficacy of vitamin D in psoriasis management potentially through TLR expression implicates a role for vitamin K in psoriasis management. Additional research is needed to determine the role of vitamin K on epidermal TLR expression.

There is mounting anecdotal evidence of the use of oral vitamin K2 combined with vitamin D supplementation on psoriasis management, yet there is a lack of evidence in the literature today. Vitamin K is well documented as a vitamin with anti-inflammatory potential. Although specific studies on the effects of vitamin K in psoriasis do not exist, the probable positive effect of its supplementation in psoriasis is supported by the documented decrease in TLR expression with oral vitamin K supplementation. A decrease in TLR expression mediated by oral vitamin K supplementation could be a potential benefit in psoriasis patients. Research is also lacking in vitamin K deficiency in psoriasis.

Deficiency data would support its role in disease management. While the implicit evidence exists, direct research on the effects of vitamin K and possible deficiency in psoriasis is required.

Conclusion

Vitamin A and D have mounting evidence in favor of existing deficiencies in psoriasis patients. These vitamins are mainstays of therapy which supports a mechanism of deficiency in the disease process. Several studies have demonstrated clear pathways for disease improvement at the cellular level with topical or oral therapies. Vitamin E has also shown efficacy at the cellular level, but lacks research supporting a deficiency in psoriasis. The current vitamin K research implicates a cellular, anti-inflammatory pathway which implicates its role in psoriasis management. Further research is needed on vitamin K to determine the potential benefit of supplementation in psoriasis patients. The favorable safety profile and low cost of fat soluble vitamin supplementation provides significant potential benefit for psoriasis patients. Despite current evidence, more research is needed to establish the role and importance of deficiencies of fat soluble vitamins and vitamin supplementation to be considered more than an adjunct therapy.

Conflicts of Interest

This research did not receive financial support or benefits from commercial sources. We have no financial interests that would create potential conflict of interest or the appearance of a conflict of interest with this work.

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