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See related article on pg 2078

Vitamin D Prevents Sunburn: Tips for the Summer?

Daniel D. Bikle

In the article by Scott et al, a high dose of vitamin D attenuated the inflammatory response to UV radiation in a small group of normal volunteers. The best results were in those subjects who had the greatest increase in circulating 25hydroxyvitamin D. Using microarray analyses these subjects showed a reduction in the expression of inflammatory markers with an increase in markers of skin barrier repair.

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The redness, pain, and swelling of the skin resulting from overexposure to sunlight is a common experience. Sunburn is caused by the UV component of sunlight, which is further separated into UVA and UVB. UVA comprises 95% of UVR from the sun. The wavelengths for UVA (320-400nm) can penetrate to the dermis, whereas UVB (5% of solar UVR), with wavelengths between 280-320, do not reach the dermis, but with their higher energy exert more damage to the epidermal structures including the DNA of the keratinocytes. Both components contribute to the erythema that

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Clinical Implications

- The inflammatory response of the skin to UV radiation was ameliorated by administration of high doses of vitamin D.
- Subjects who responded best to the protective actions of vitamin D showed increased expression of arginase-1.
- Arginase-1 is highly expressed in myeloid derived suppressor cells, so its increased expression by vitamin D may contribute to the protective actions of vitamin D.

accompanies sunburn, but UVB appears to be the primary activator of the inflammatory response through activation of inflammasomes leading to the release of cytokines, chemokines and reactive oxidation species (Feldmeyer et al., 2007; Nasti and Timares, 2012).

Chronic exposure to UVB (and UVA) is the major cause of skin cancer and photoaging. However, UVB is responsible for the cleavage of the B ring in 7-dehydrocholesterol to form pre vitamin D_3, which then undergoes thermal mediated isomerization to vitamin D_3. The energy required for this photoreaction is 18mJ/cm2 in males with class III pigmentation (Matsuoka et al., 1989). Furthermore, the skin can metabolize the vitamin D3 it produces to the active hormonal form, $1,25(OH)_2D_3$ (Bikle et al., 1986). This enzymatic process, mediated by CYP27B1, is stimulated by cytokines such as IFN−γ and TNF-α (Bikle et al., 1991), cytokines the release of which is stimulated by UVR in the epidermis (Muthusamy and Piva, 2009). Vitamin D via its active metabolite $1,25(OH)_2D$ has anti-inflammatory actions and may be protective against UVR-induced tumor formation (Bikle, 2015).

$1,25(OH)_2D$ has both direct and indirect effects on the regulation of a number of cytokines involved in the inflammatory response. For example, $1,25(OH)_2D$ suppresses the inflammatory and T-cell stimulatory actions of macrophages through stimulation of IL-10 (Korf et al., 2012). Moreover, $1,25(OH)_2D$ blocks IL-1β induction of RANKL, TNF-α, and IL-6 in human synoviocytes (Feng et al., 2013). $1,25(OH)_2D$ suppresses IFNγ, via a negative vitamin D response element (VDRE) in the IFNγ promoter. NFκB signaling is blocked by $1,25(OH)_2D$ by stimulating IκBα expression and inhibiting its activation of IL-1, 8 and 12. $1,25(OH)_2D$ suppresses relB expression by stimulating the binding of an HDAC3 inhibitor complex to its promoter. Thus $1,25(OH)_2D$ has numerous means to suppress the inflammatory response (Bouillon et al., 2008).

VDR agonists have been shown in animal studies to suppress a wide variety of inflammatory diseases including diabetes mellitus, arthritis, psoriasis, systemic lupus erythematosis, experimental allergic encephalitis, inflammatory bowel disease and thyroiditis (Bikle, 2014). Epidemiologic studies have found an association between low 25OHD levels and increased markers of inflammation (Amer and Qayyum, 2012; Bellia et al., 2013). However, randomized clinical trials examining the potential for vitamin D supplementation in the management of inflammatory diseases have been mixed (Cannell et al., 2014). In the meta-analysis of these randomized clinical trials Cannell et al. (2013) noted that those trials examining more inflammatory conditions were more likely to show benefit, but that none of the trials used pharmacologic doses of vitamin D. Of the reviewed trials in this meta-analysis, skin conditions were not included, although psoriasis is a well-established example of an inflammatory disease treatable with vitamin D analogs.

The study by Scott et al. (2017) in this issue examines the potential for a pharmacological dose of vitamin D to prevent the inflammatory response to UVR. This was a small study (20 subjects) in which the subjects were given a placebo or one of three doses of vitamin D_3 (50,000 IU, 100,000 IU, 200,000 IU) 1hour after exposure to UVR. UVR was administered using a xenon arc lamp that delivered a spectrum comparable to sunlight sufficient to result in 1, 2, or 3 MED (minimal erythema dose) that had been predetermined prior to the actual study. The degree of erythema was determined. Skin biopsies were then obtained at different times up to one week post UVR to assess the histologic appearance and provide RNA for microarray analyses. Blood was obtained to measure the levels of 25OHD, $1,25(OH)_2D$, and $24,25(OH)_2D$. The authors demonstrated increasing epidermal changes with increasing doses of UVR, and increasing serum concentrations of the vitamin D metabolites with increasing doses of vitamin D as expected. Surprisingly, UVR per se did not increase the circulating levels of these vitamin D metabolites in those subjects receiving the placebo. The most significant results were achieved in the group exposed to the highest level of UVR and highest dose of vitamin D. This group had significant suppression of erythema and histologic changes associated with UVR compared to the placebo treated controls. Moreover, these subjects had decreased expression of TNF-α and iNOS following UVR compared to the placebo treated controls, consistent with the reduction in inflammation. The authors did not look for evidence of DNA damage, the presumed etiology for tumor formation, but their goal was more short term—prevention of sunburn. The results from the microarray analyses were quite interesting in that response patterns segrated into two clusters. Cluster 1 patterns were enriched for barrier repair genes that were down regulated while genes involved in inflammation were upregulated, whereas cluster 2 patterns were enriched for genes with the opposite effects. Subjects who had the greater response to vitamin D supplementation with respect to increases in circulating 25OHD levels tended to have microarray results in cluster two. All of the subjects receiving the placebo had skin samples that fell into cluster one, but so did some of the subjects who received the vitamin D supplement, but had a blunted response.

One of the genes whose expression was increased in cluster 2 was arginase-1. Although this gene is probably best known for its role in the urea cycle, it is also highly expressed in myeloid derived suppressor cells (Kwak et al., 2015). These cells are found in murine tumor models and models of

inflammation. They inhibit T-cell mediated inflammation at least in part by increasing the number of Treg cells. The authors suggest that vitamin D, presumably via $1,25(OH)_2D$, induces this gene, although it is equally plausible that the response to vitamin D is indirect. Regardless, this would be a novel action of vitamin D and could contribute both to the inhibition of inflammation and tumor formation by vitamin D. Although this study focused on the ability of pharmacologic doses of vitamin D to suppress the inflammation caused by UVR, the results may suggest a potential for vitamin D to suppress tumor formation, although the administration of 200,000 IU vitamin D for an extended period cannot be recommended.

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CONFLICT OF INTEREST
The authors state no conflict of interest.

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New Evidence Supporting Cyclosporine Efficacy in Epidermal Necrolysis

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Sixty years after its original description by Sir Alan Lyell, epidermal necrolysis (from Stevens-Johnson syndrome to toxic epidermal necrolysis) seems finally amenable to a specific treatment in addition to essential symptomatic measures in specialized settings. A recently published systematic review and an article by Gonzales-Herrada et al. strongly suggest that cyclosporine is effective in reducing the risk of death.

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Epidermal necrolysis (EN), including Stevens-Johnson syndrome, toxic epidermal necrolysis, and overlapping forms, is a rare but very severe cutaneous adverse reaction most often due to medications. In a European prospective cohort, the overall mortality for all subgroups considered together was 22% at 6 weeks and 34% at 1 year (Sekula et al., 2013).

Over decades, many small studies reported the empiric use of high-dose corticosteroids, cyclophosphamide, plasma exchanges, and anti-tumor necrosis factor-α monoclonal antibodies as specific measures that halted the progression of lesions. More recent studies recommended high doses of intravenous immunoglobulins (IVIg). Each of these interventions was supported by the enthusiasm of their promotors and in some cases their funders, but subsequent critical reviews and/or meta-analyses did not confirm efficacy.

Treatment recommendations for EN issued by burn units in the United States, the Health Minister in France, and the British Association of Dermatologists (Creamer et al., 2016) were that no etiologic treatment was efficacious and that supportive measures in burn units or other specialized departments (in Europe including departments of dermatology and intensive care units) were the best

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