

Vitamin D is no substitute for the sun

Yoshiaki Matsushima, MD,^a Kento Mizutani, MD,^a Yukie Yamaguchi, MD, PhD,^b and Keiichi Yamanaka, MD, PhD^a *Tsu and Yokohama, Japan*

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Let us take a moment to envision our patients who are new, perhaps first-time, parents and have a history in common of serious allergic disease, such as atopic dermatitis or asthma. They are understandably eager that their newborn baby not experience their symptoms, and should such symptoms arise, especially when their child is in infancy, the parents feel at a loss and at fault. Yet although heredity is one factor in an infant's susceptibility to allergic disease, studies have shown that environmental factors can modify both risk and severity. Recent research has demonstrated, for example, that the application of moisturizer from week 1 to week 32 of life can decrease the occurrence of atopic dermatitis or eczema during that period.¹

The skin is one of our most important immune organs, a concept illustrated by a framework known as skin-associated lymphoid tissue. Once activated, this complex system produces and releases large amounts of inflammatory cytokines. These cytokines induce prolonged cutaneous and systemic inflammation, placing patients with eczema^{1,2} and psoriasis, which is one of the more intractable skin disorders, at increased risk for cardiovascular and cerebrovascular complications. We conceptualize this chain of events as the inflammatory skin march.³ An inflammatory cycle establishes and accelerates, resident memory T cells live longer inside the skin,⁴ and when keratinocytes are irritated or activated, skin eruption reoccurs frequently. Once in place, such a

cycle is difficult to impede, but early intervention can inhibit its progression.

In the current issue Rueter et al⁵ demonstrate an association between direct UV light exposure in the first 3 months of life and both a decreased incidence of medically diagnosed infant eczema and controlled levels of immune factors associated with allergic inflammation at age 6 months. The authors have reported that greater UV light exposure was associated with decreased PBMC production of IL-2, which contributes to the differentiation of naive CD4 T cells into T_H2 cells, and decreased levels of GM-CSF, which facilitates antigen-specific T_H2 responses and allergic inflammation. Their findings further associate greater UV light exposure with lower levels of eotaxin, a chemokine associated with allergic inflammation. In sum, free and easily accessible UV light exposure can stabilize the aberrant or excessive immune responses of PBMCs and result in UV-induced immunomodulation.

Control of the hematologic immune response by suppressing skin disease can also be observed in the treatment of psoriasis with biologics: patients with severe types of psoriasis experience increased activation of neutrophils and monocytes within a skin and blood inflammatory cycle that biologic therapy can stabilize.⁶ The current study might raise questions about immune suppression resulting from decreased PBMC cytokine production in the group with high sun exposure, but use of antibiotics against infection during the observation period did not increase among these infants. A long-term observation study will lead to final conclusions.

The exact reason why UV light exposure suppresses skin inflammation independent of vitamin D3 application or plasma vitamin D3 concentration is obscure. Of course, the thin skin of an infant lends itself to penetration by UV light. UVA phototherapy induces regulatory T-cell production, and there is some evidence that direct suberythral UV radiation can upregulate the synthesis of significant stratum corneum lipids, including free fatty acids (Fig 1).⁷

In several countries skin whitening is of cultural and aesthetic importance for many, and for this reason and others, parents will protect their new baby from such exposure. However, this tendency might be exerting a negative effect in terms of allergy development. It should be noted that vitamin D3 selectively downregulates the expression of cutaneous lymphocyte-associated antigen, a surface glycoprotein expressed by skin-homing T cells. Topical application of vitamin D3 decreases lymphocyte migration/invasion patterns to the skin and leads to suppression of skin inflammation,⁸ and such application is clinically used for the treatment of psoriasis. In the current study oral supplementation of vitamin D3 showed no contribution to suppression of allergic symptoms.⁵ This might be because the concentration of vitamin D3 in the skin or draining lymph nodes, where lymphocytes are residing and maturing, was insufficient to affect cutaneous lymphocyte-associated antigen reduction.

From ^athe Department of Dermatology, Mie University, Graduate School of Medicine, Tsu, and ^bthe Department of Environmental Immuno-Dermatology, Yokohama City University Graduate School of Medicine, Yokohama.

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Corresponding author: Keiichi Yamanaka, MD, PhD, Department of Dermatology, Mie University, Graduate School of Medicine, 2-174 Edobashi, Tsu, Mie 514-8507, Japan. E-mail: yamake@clin.medic.mie-u.ac.jp.

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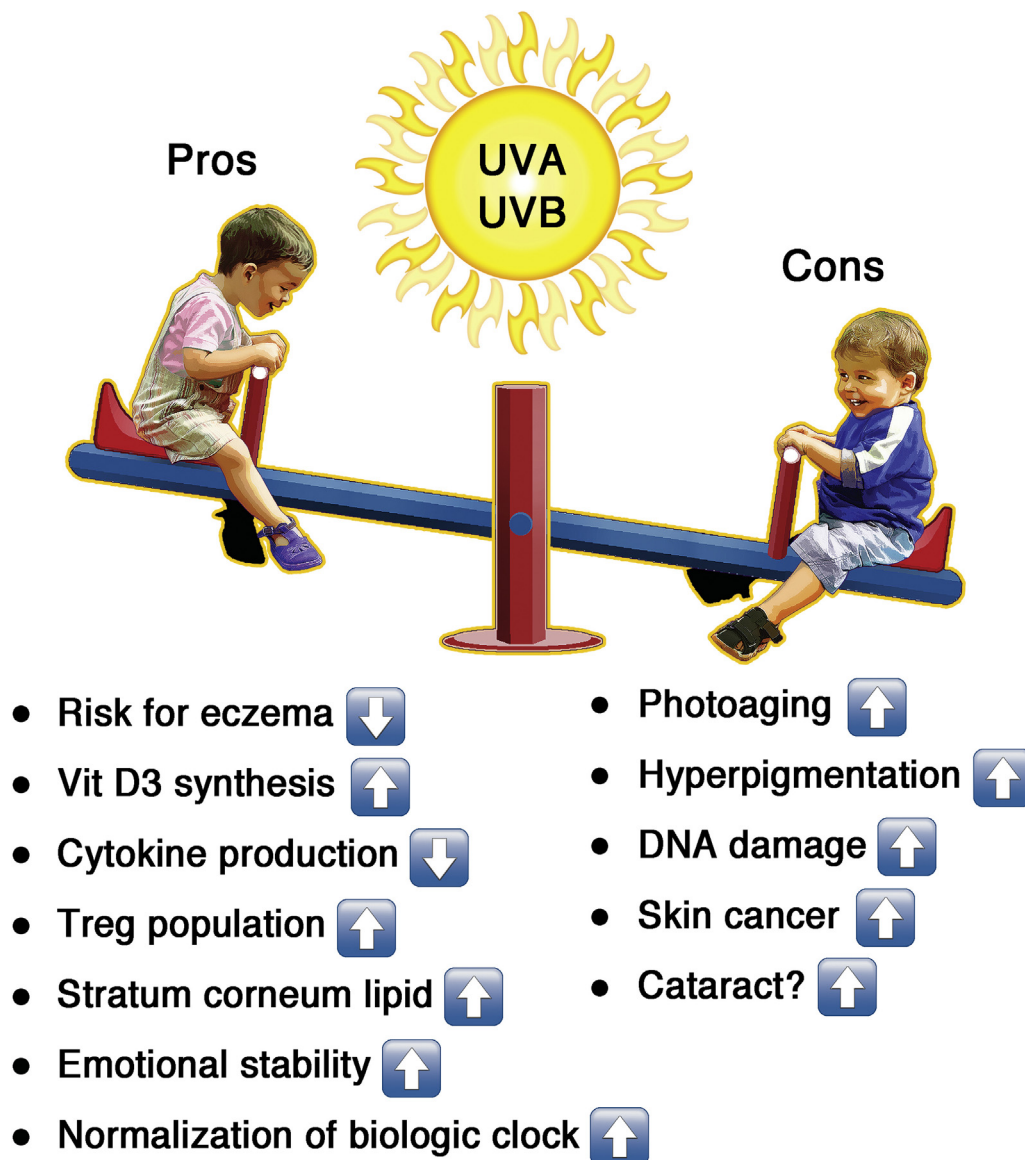


FIG 1. Pros and cons of sun exposure. Although the complications for photoaging, hyperpigmentation, and increased risk for skin cancer are a concern, there are abundant beneficial points, including a decreased risk for eczema and increased vitamin D3 (*Vit D3*) synthesis and regulatory T (*Treg*) cell populations.

Is the prevalence of atopic dermatitis in tropical geographic areas lower compared with that in countries with low UV light exposure? This theory is not applicable for all areas (International Study of Asthma and Allergies in Childhood Phase 3 trial database, <http://isaac.auckland.ac.nz/phases/phasethree/results/results.php>) because of possible factors affecting the occurrence of allergic disorders: genetic background, infection, air pollution, and the effect of UV exposure can be counteracted, suggesting the observed immunomodulatory effect reported in the current issue might be a transient phenomenon.

In summary, Reuter et al⁵ report that PBMC production of inflammatory cytokines was lower in those infants who had greater UV light exposure compared with those who had less exposure. It is possible that UV in sunlight initially directly suppresses skin inflammation and then blocks inflammatory cycles that result in systemic inflammation.³ Further work will determine a

recommended optimal dose of sun exposure to avoid photoaging, hyperpigmentation, and skin cancer.

Certainly, sun exposure comes with complications: photoaging is characterized by epidermal thickening, especially the stratum corneum with atypical, dysplastic, and vacuolized keratinocytes, and tangled and granular amorphous elastin structures thicken dermal connective tissue. Hyperpigmentation after solar UV exposure comprises an immediate tanning reaction and delayed formation of new melanin.⁹ In addition, skin cancer, including squamous cell carcinoma or malignant melanoma, is associated with UV-induced DNA damage/mutations (Fig 1). In the study at hand, however, the occurrence of allergic symptoms was consistent regardless of season of birth in the group with sun exposure, suggesting a minimum dosage of UV exposure in the winter season might be sufficient to suppress immunologic reactions. Multicentric trials and long-duration

observations will be required to clarify optimal results and recommendations.

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