Uses of vitamins A, C, and E and related compounds in dermatology: A review

Karen Laszlo Keller, MD, Neil A. Fenske, MD, FACP

Abstract
Vitamins have been increasingly used as prophylactic and therapeutic agents in the management of skin disorders. The current literature is replete with studies that promote the potential benefits of these compounds and attempt to elucidate their mechanisms of action. We review the literature and discuss the roles, safety, and efficacy of vitamins A, C, and E and related compounds in cutaneous health and disease.
Vitamins A, C, and E and related compounds are valuable agents in the prophylaxis and treatment of photoaging, skin cancer, and numerous skin disorders. These vitamins are related, in part, through their ability to act as antioxidants. Antioxidants stabilize reactive, potentially harmful, free radicals generated after UV exposure and during normal and pathological metabolic processes. If not quenched, these free radicals contribute to photoaging and photocarcinogenesis by producing DNA mutations. In addition to acting as antioxidants, these compounds are modulators of skin disorders through other mechanisms of action. We review vitamins A, C, and E and related compounds in cutaneous health and disease.

**VITAMIN A (RETINOL)**

Vitamin A is present in yellow and green vegetables, egg yolk, butter, liver, and fish oils. Stored in the liver, vitamin A supplies increase with increasing age. Retinoids include the natural and synthetic derivatives of vitamin A that are structurally related to the parent compound, such as retinol (vitamin A aldehyde), retinyl esters, and retinoic acid (tretinoin). The term retinoid was originally applied to a group of compounds that produce biologic responses via a specific receptor whose usual bindings are retinol and retinoic acid. Retinoids are derived from retinyl esters in dietary animal sources and from carotenoids in yellow and leafy green vegetables.

Retinoids have many important biologic effects: regulating growth and differentiation in epithelial cells, inhibiting tumor promotion during experimental carcinogenesis, diminishing malignant cell growth, decreasing inflammation, and enhancing the immune system. Retinoic acid treatment decreases the total keratin content of keratinocytes and changes keratin expression patterns. During terminal differentiation, retinoic acid interferes with cornification by suppressing the expression of epidermal transglutaminase, an enzyme crucial to the cross-linking and formation of the cornified cell envelope.

*Photodamage/photoaging*

The most thoroughly researched topical retinoid is trans-retinoic acid or tretinoin, which has been used to treat acne since 1971. Kligman et al first noted tretinoin’s ability to improve photoaged skin in mice; human and in
vivo studies confirmed that retinoic acid enhances naturally occurring reparative processes in photodamaged skin.\textsuperscript{6, 7} Multiple controlled studies have shown that topical tretinoin improves fine and coarse wrinkling, diminishes tactile roughness, lightens solar lentigines, and reduces the number and size of actinic keratoses.\textsuperscript{6, 7, 8, 9, 10} Pepine et al\textsuperscript{11} reviewed the clinical and histologic effects of topical tretinoin on photodamaged skin. The epidermal effects include a reduction of stratum corneum cohesion, epidermal hyperplasia, amorphous intercellular and intracellular material, tonofilaments, desmosomes, melanosomes, and melanin production and increased Langerhans cells. The dermal effects include increased production of collagen, tropoelastin, fibronectin, and angiogenesis and decreased glycosaminoglycans, collagenase, and gelatinase.\textsuperscript{11}

In a dose-reduction study involving 126 patients, Olsen et al\textsuperscript{12} found that thrice-weekly applications of tretinoin emollient cream 0.05% after 48 weeks of daily use maintained reductions in photodamage. Patients who decreased therapy to once weekly or discontinued therapy experienced a reversal of beneficial effects.

Duell et al\textsuperscript{13} studied topical retinol, a retinoid weaker than retinoic acid, and found unoccluded topical retinol to have increased penetration compared with unoccluded retinoic acid, without the irritation caused by retinoic acid. These investigators concluded that the low irritancy and potent retinoid activity may allow retinol to become a clinically useful product.

Griffiths et al\textsuperscript{14} conducted a vehicle-controlled trial on 38 Asian women with facial melasma who applied 0.1% tretinoin cream daily for 40 weeks. Sixty-eight percent of these patients showed improvement or marked improvement compared with 5% in the vehicle group; epidermal pigment decreased by approximately 36%.

\textbf{Skin cancer}

Synthetic retinoids such as tretinoin, isotretinoin, and etretinate have been studied in many premalignant and malignant skin conditions, such as actinic keratoses,\textsuperscript{15, 16} squamous cell carcinomas,\textsuperscript{17, 18, 19} Bowen’s disease,\textsuperscript{17} basal cell carcinomas,\textsuperscript{18, 20, 21} keratoacanthomas,\textsuperscript{22} porokeratoses,\textsuperscript{17} epidermodysplasia verruciformis,\textsuperscript{23} oral leukoplakia,\textsuperscript{24} melanoma,\textsuperscript{25} and cutaneous T-cell lymphomas.\textsuperscript{18} Retinoids probably do not cure skin cancer, although treatment may prevent the formation of new lesions as long as therapy is continued.

Lippman et al\textsuperscript{18} reviewed reports of retinoid-treated skin cancers and found
that 51% of 57 patients with basal cell carcinomas and 71% of 14 patients with advanced squamous cell carcinomas responded partially or completely to oral retinoids. In a controlled prospective study of 5 patients with xeroderma pigmentosum, Kraemer et al.\textsuperscript{19} found high-dose oral isotretinoin 2 mg/kg/d decreased the yearly incidence of new basal and squamous cell carcinomas. When treatment was discontinued, the tumor incidence rate increased towards that of pretreatment rate within a few months. Tangrea et al.\textsuperscript{20} performed a 3-year multicenter trial testing the efficacy of oral isotretinoin 10 mg/d versus placebo in preventing new skin cancers in 981 patients with a history of basal cell carcinoma; there was no difference in the percentage of patients with new basal cell cancers or yearly rates of new basal cell cancer formation in the 2 groups. Levine and Meyskens\textsuperscript{25} described 2 patients with cutaneous metastatic melanoma who were treated with retinoic acid 0.05% solution under occlusion for 12 weeks, with complete and partial regression of lesions.

Other studies have shown that etretinate 0.5 to 1 mg/kg daily has induced complete regression of actinic keratoses, basal cell carcinomas, and keratoacanthomas.\textsuperscript{22, 23, 24, 25, 26} Rook et al.\textsuperscript{27} treated 4 patients who had undergone renal transplantation with daily topical tretinoin 0.025% cream and oral etretinate 10 mg, and 4 patients with topical tretinoin alone. By 6 months, 3 of 4 patients receiving the combination therapy had more than a 50% suppression of neoplastic growths, and 3 of 4 in the other group had a “substantial benefit.” Hudson-Peacock et al.\textsuperscript{28} used etretinate 0.3 to 1.0 mg/kg/d to treat 4 patients with psoriasis with PUVA-induced keratoses and found the number of keratoses decreased within 2 weeks of initiating therapy, with rapid reappearance of keratoses after discontinuing etretinate.

\textit{Wound healing}

Patients whose bodies are vitamin A deficient experience diminished wound healing, correctable by vitamin A supplementation.\textsuperscript{29} Many studies have shown that supplemental vitamin A prevents or restores impaired wound healing caused by corticosteroids and other medications.\textsuperscript{30, 31, 32, 33} Vitamin A, administered with glucocorticoids, can reverse deleterious effects on wound healing.\textsuperscript{30} Vitamin A may enhance wound healing by promoting an early inflammatory response\textsuperscript{34} and by increasing epithelialization, collagen synthesis, fibroplasia, and angiogenesis.\textsuperscript{35}

\textit{Acne/Rosacea}

A side effect of vitamin A, suppression of keratinization, can be used in the
treatment of acne. When lesions are dry or hyperkeratotic and minimally inflamed, doses of 100,000 to 300,000 IU/d of vitamin A may be tried.\textsuperscript{36} Topical retinoic acid, or tretinoin, normalizes keratinization of the pilosebaceous unit and prevents obstruction of the follicular unit. Thus tretinoin is most effective against comedonal acne.

Tazarotene, a synthetic acetylenic retinoid prodrug that converts to the active metabolite tazarotenic acid, is readily eliminated without adipose tissue storage.\textsuperscript{37} Tazarotene normalizes the abnormal differentiation and proliferation of keratinocytes, that may contribute to decreased corneocyte accumulation and cohesion. In patients with acne, tazarotene 0.1 \% and 0.05\% topical gels significantly decreased acne lesions more than in control patients. The higher strength was more effective and more irritating.\textsuperscript{38}

Adapalene, a synthetic naphthoic acid retinoid, has similar actions to that of retinoids, with moderate to potent anti-inflammatory activity.\textsuperscript{39} In studies of patients with acne, adapalene 0.1\% gel was as effective as tretinoin 0.025\% gel against open and closed comedones and more effective against inflammatory lesions, with significantly less irritation.\textsuperscript{40}

Oral isotretinoin inhibits sebaceous gland activity,\textsuperscript{41} inhibits \textit{Propionibacterium acnes} growth in the follicle,\textsuperscript{42} alters keratinization,\textsuperscript{43} and suppresses inflammation.\textsuperscript{41} Oral isotretinoin reduces sebum excretion by approximately 90\% within 1 month in doses of 0.5 to 2.0 mg/kg/d.\textsuperscript{44, 45} In contrast, the aromatic retinoid etretinate suppresses sebum production in approximately 30\% of patients.\textsuperscript{46} After treatment is completed, quantitative sebum production returns toward pretreatment levels; however, 20 to 99 weeks after treatment, there is a persistent 38\% inhibition overall.\textsuperscript{45} The sebaceous units convert to epithelial buds, \textit{P acnes} diminishes, and ductal cornification decreases.\textsuperscript{41, 47} In addition to anti-inflammatory effects, isotretinoin probably has a direct effect on comedogenesis.\textsuperscript{48}

Most clinical trials have shown severe acne to be responsive to oral isotretinoin with a 4- or 5-month course at doses of 0.5 to 2.0 mg/kg/d.\textsuperscript{43} An increase of acne cysts may occur within the first few weeks of therapy, although a 50\% decrease in acne cysts on the face usually occurs at 8 weeks of therapy and on the trunk at 12 weeks. Residual acne continues to improve after completion of the therapeutic course. Of the patients whose condition clears, most remain free of cysts. Relapses that require another course of isotretinoin occur in approximately 10\% to 40\% of patients with acne.\textsuperscript{49} After a 2-month treatment-free period, a second course of therapy may be initiated, often in a higher dose, such as 1.5 to
2.0 mg/kg/d for an additional 4 to 6 months.

Plewig et al. treated 13 patients with severe rosacea with isotretinoin 0.5 to 1.0 mg/kg/d for 12 to 28 weeks and noted a marked decrease in lesion counts, erythema, edema, telangiectasias, and rhinophyma. These patients remained in remission after 15 months. The same investigators treated 13 patients with gram-negative folliculitis and reported a marked response to isotretinoin therapy. Ertl et al. evaluated 20 patients with rosacea who were divided into 3 treatment groups: isotretinoin 10 mg daily, topical tretinoin 0.025% cream, or a combination. After 16 weeks of therapy, all 3 groups had a significant decrease in papules and pustules, with no intensification of erythema and no complaints of excessive stinging, burning, or dryness.

Psoriasis

Etretinate 0.5 to 1.0 mg/kg/d has been the retinoid of choice in the treatment of pustular and erythrodermic psoriasis and psoriatic arthritis. The dosage for erythrodermic psoriasis is often started at 25 to 35 mg/d and increased to 50 to 60 mg/d within 2 to 4 weeks, although pustular psoriasis may require an initial dose of 75 mg/d. Psoriasis may worsen during therapy initiation. Etretinate is used to enhance the response to photochemotherapy with oral methoxsalen and UV radiation (UVA 320 to 400 nm) or PUVA. In this regimen, called Re-PUVA, etretinate may be given for 1 to 4 weeks followed by PUVA; it is often effective in patients whose condition is unresponsive to either therapy alone. Because of the lower dose of etretinate needed, fewer side effects from the drug are noted than when used alone.

Acitretin, the major metabolite of etretinate, has replaced etretinate for the treatment of severe psoriasis. Etretinate is approximately 50 times more lipophilic than acitretin and is stored and slowly released from adipose tissue. Thus the elimination half-life of etretinate is more than 100 days, whereas that of acitretin is approximately 2 days. After etretinate therapy, the drug may be detected in serum for 2 or more years; whereas after acitretin therapy, the drug becomes undetectable after 3 to 4 weeks. Acitretin may convert back to etretinate, most notably when alcohol is consumed. Acitretin and etretinate have comparable efficacy and side effects in the treatment of psoriasis. Olsen et al. conducted an 8-week double-blind, placebo-controlled study in 15 patients comparing acitretin 25 or 50 mg/d with placebo in patients with moderate to severe psoriasis. All patients showed moderate improvement in erythema, scaling, and induration, with an optimal dose of 50 mg/d. Therapy is initiated at 25 to 50
mg/d, with maintenance doses of 25 to 50 mg/d until lesions have resolved. Patients may not see the full benefit of acitretin until after 2 or 3 months of therapy. Because of its teratogenicity, 2 forms of reliable birth control are recommended to be used concurrently for at least 1 month before, during, and 3 years after therapy in women of child-bearing potential. A negative serum pregnancy test is required within 2 weeks of initiating therapy, and a complete blood count with differential, liver function tests, and serum lipids (triglycerides, cholesterol) are usually obtained before treatment and at 1- to 2-week intervals until stabilization. Alcohol should be avoided during therapy and for 2 months after therapy.60

Tazarotene normalizes keratinocyte differentiation and proliferation and decreases inflammation by decreasing the expression of inflammatory markers on keratinocytes.51 Tazarotene 0.05% and 0.1% gels are effective in treating mild to moderate plaque psoriasis not exceeding 20% of total body surface area. Compared with twice-daily fluocinonide cream, once-daily tazarotene produces similar reductions in plaque elevation and similar treatment success rates. Although fluocinonide demonstrates a greater reduction in erythema, tazarotene gel once daily produces a more prolonged therapeutic effect, with significant improvements lasting up to 12 weeks after cessation of therapy. Side effects include mild to moderate local irritation, pruritus, burning, or erythema.62

Lichen planus

Patients with recalcitrant or severe lichen planus have been successfully treated with isotretinoin 0.25 to 0.5 mg/kg/d,63 etretinate 0.3 to 0.6 mg/kg/d,63 and acitretin 0.25 to 0.75 mg/kg/d,64, 65 with marked improvement or remission in 64% to 83% of patients.

Cutaneous lupus erythematous

Retinoids have been successful in the treatment of refractory cutaneous lupus erythematous. Etretinate 0.5 to 1.0 mg/kg/d, isotretinoin 0.5 to 1.0 mg/kg/d, and acitretin 50 mg/d have each been shown to improve cutaneous lesions.66, 67, 68, 69, 70, 71

Disorders of keratinization

Vitamin A and its derivatives, etretinate and isotretinoin, cause variable improvement in keratinizing disorders such as Darier’s disease, lamellar ichthyosis, and nonbullous congenital ichthyosiform erythroderma.72, 73 Blanchet-Bardon et al74 found better results and similar side effects with
acitretin than with etretinate in patients with nonbullous congenital ichthyosiform erythroderma, lamellar ichthyosis, and Papillon-Lefevre syndrome. They recommend a starting dose of 30 to 35 mg/d in adults and 0.7 mg/kg/d in children or adolescents.

Goldsmith et al\textsuperscript{73} found that a several-month course of oral isotretinoin 1 to 2 mg/kg/d may produce extended remission or cure of pityriasis rubra pilaris. Etretinate and acitretin have also been used with positive results.\textsuperscript{74, 75, 76} Cohen and Prystowsky\textsuperscript{76} found that the condition of patients with pityriasis rubra pilaris cleared faster with etretinate than with isotretinoin. Although vitamin A 300,000 to 500,000 IU daily may be effective, treatment is often limited by an increased risk of hypervitaminosis A and a high relapse rate.

\textit{Striae}

Elson\textsuperscript{77} conducted a 12-week study of 20 patients who applied various strengths of tretinoin daily to striae and found tretinoin 0.1\% cream most effective. Kang et al\textsuperscript{78} found that 8 of 10 patients with early striae improved markedly with 0.1\% tretinoin daily for 6 months. Pribanich et al\textsuperscript{79} conducted a double-blind prospective study of 11 patients with striae who applied either tretinoin 0.025\% cream or placebo daily for 7 months, with no difference between the groups.

\textit{Safety}

Although less severe, the acute toxicities of the synthetic retinoids, isotretinoin and etretinate, are similar to the acute toxicities of high doses of vitamin A. Acute side effects involve mainly the skin and mucous membranes and include cheilitis, facial dermatitis, dry mucous membranes, stratum corneum fragility, sticky skin, conjunctivitis, palmoplantar peeling, alopecia, pyogenic granuloma–like lesions in acne, paronychia, and corneal opacities. Systemic toxicities include hypertriglyceridemia, liver function test elevations, arthralgias, pseudotumor cerebri, depression, and teratogenicity.

Although high doses of vitamin A can have acute, reversible side effects, chronic intake of a dose exceeding 50,000 IU has been associated with headache, nausea, and irreversible bone changes such as demineralization, thinning of long bones, cortical hyperostosis, periostosis, and premature closure of epiphyses.\textsuperscript{80, 81, 82} Several case reports have documented birth defects associated with a vitamin intake at or above 25,000 IU daily.\textsuperscript{83} Bendich and Langseth\textsuperscript{80} reviewed recent controlled
studies that found no potential human teratogenicity associated with supplemental vitamin A intakes at the recommended levels of 5000 IU for all population groups, including women of childbearing potential; 8000 IU appeared to be safe for pregnant women.

Johnson et al. performed a prospective study of 284 healthy women, comparing no supplementation with a daily intake of vitamin A, 1250 to 25,000 IU, for 5 years. Serum retinyl ester levels and serum liver enzyme levels did not differ in the 2 groups.

**BETA-CAROTENE**

Beta-carotene is present in green leafy vegetables, carrots, sweet potatoes, squash, cantaloupes, meat, butter, and cheese. Synthetic beta-carotene absorption is enhanced when administered with a fatty meal. Beta-carotene is a precursor to vitamin A (retinol) and naturally functions as a free radical scavenger, protecting cell membranes from lipid peroxidation and plants from UV light-induced damage. In humans, oral beta-carotene increases peripheral blood levels of CD4+ helper T lymphocytes and natural killer cells.

Although beta-carotene inhibits the development of chemically and UV light–induced skin cancers in animals, many human studies have shown no benefits. Beta-carotene moderately reduced UV erythema in some studies but had no effect in others.

Mathews-Roth et al. used beta-carotene to treat 133 patients with erythropoietic protoporphyria (EPP) and found that 84% experienced an increase in their tolerance to sunlight. They recommend a starting dose of 180 to 300 mg/d for patients aged 16 years and older, 150 to 180 mg/d for patients aged 13 to 15 years, 120 to 150 mg/d for patients aged 9 to 12 years, 90 to 120 mg/d for patients aged 5 to 8 years, and 60 to 90 mg/d in children aged 1 to 4 years. If a patient maintains a serum level of at least 800 mg/dl for 3 months with no increased tolerance to sunlight, beta-carotene should be discontinued. Pollitt reported that 42 of 44 patients with EPP who were treated with beta-carotene had benefit ranging from “improved” to “transformed life.” However, one controlled trial of beta-carotene in patients with EPP showed no significant improvement over placebo, although critics emphasized the negative results resulted from the low dose of beta-carotene used.

**Safety**
Beta-carotene has been used at dosages exceeding 180 mg/d chronically without the development of abnormally high levels of serum vitamin A or evidence of hypervitaminosis A. Patients taking 30 mg or more of beta-carotene for extended periods of time may experience the development of a reversible carotenoderma, noticeable when the serum level is 3 to 4 times normal. This harmless condition may be differentiated from jaundice by the lack of scleral and nail involvement.

**VITAMIN C (ASCORBIC ACID)**

Vitamin C in the active form is called L-ascorbic acid and is present as ascorbate, a water-soluble molecule, in most biologic settings. Vitamin C, present in vegetables and citrus fruits, is not synthesized by the body and is the most important antioxidant in extracellular fluids and in many cellular activities.

Ascorbic acid acts as an antioxidant by scavenging and quenching free radicals and by regenerating vitamin E from its radical form. Ascorbic acid may also act as a pro-oxidant in the presence of transition metal ions, such as iron. In rat studies, Wefers and Sies showed that in the presence of sufficient amounts of vitamin E, the pro-oxidant effect of ascorbic acid is shifted to an antioxidant effect, thus allowing ascorbic acid to act as a protective agent.

*Photodamage/photoaging*

UV radiation generates free radicals that damage cell membranes, various enzymes, and DNA. Therefore the antioxidant vitamin C may effectively interfere with UV-induced generation of reactive oxygen species, because it reacts with or suppresses the superoxide anion, the hydroxyl radical, and singlet oxygen. By replenishing vitamin E, vitamin C indirectly inhibits lipid peroxidation. In mice, Dunham et al found that increases in dietary vitamin C reduced UV-induced tumors. Bissett et al showed that topical vitamin E or C effectively minimized low level, chronic UVB damage to mouse skin.

Murray et al treated the volar forearms of 10 volunteers with a 10% L-ascorbic acid solution or vehicle control. After UVB irradiation, sites treated with topical vitamin C showed a significant reduction of the minimal erythema dose and a less intense erythematous response than controls.

An aqueous 10% solution of L-ascorbic acid allows delivery of pharmacologic levels of ascorbic acid to the skin. Percutaneous absorption
studies demonstrated that 12% of the ascorbic acid traversed the stratum corneum barrier in 72 hours. Darr et al investigated the effects of topical vitamin C on porcine skin. They raised skin levels of vitamin C by topical application and found markedly decreased skin levels of vitamin C after UV exposure. In other studies, human sunburn cells decreased, and improvement occurred after 3 days of UVB exposure to sites treated with 10% topical vitamin C 15 to 30 minutes before exposure. Studies demonstrated this regimen of topical vitamin C application attenuated a UVA-mediated phototoxic response.

Although vitamin C has no UV absorption spectra in the UVA (320 to 400 nm) or UVB (290 to 320 nm) range, topical vitamin C may photoprotect against UVR because of its antioxidant and anti-inflammatory properties. Roles for topical vitamin C in photoprotection and photodamage may be elucidated in future double-blind controlled studies.

Wound healing

Vitamin C is critical in wound healing, acting as a cofactor for several enzymes, including lysyl and prolyl hydroxylase, which stabilize collagen. In vitamin C deficiency, fibroblasts produce unstable collagen, providing a weak framework for repair, thus impairing wound healing. Phillips and Pinnell found that ascorbic acid counteracted a reduced proliferative capacity of elderly dermal fibroblasts in vivo. Finglas et al reported lower concentrations of plasma ascorbic acid in the elderly (aged 64 to 74 years) compared with healthy adults (aged 20 to 64 years).

Vitamin C levels are commonly low in older patients, which may contribute to slower and more difficult wound healing.

The role of supplemental vitamin C in wound healing remains controversial. Levenson and Demetriou found no evidence that wound healing is enhanced by supplemental vitamin C, although severely ill patients may benefit from supplements, because their stores are depleted. Taylor et al treated 20 patients with pressure ulcers with ascorbic acid 500 mg or placebo and found that patients with supplemental vitamin C had a reduced pressure sore area compared with controls.

Furunculosis

Levy et al treated 23 patients with recurrent furunculosis and negative nasal cultures with vitamin C 1000 mg/d for 4 to 6 weeks. The condition of 10 of 12 patients with low vitamin C levels and neutrophil dysfunction
cleared, with no lesions after 1 year; and vitamin C levels and neutrophil function normalized. Vitamin C did not affect the outcome in the control group.

Safety

Vitamin C is safe in high levels for prolonged periods due, in part, to its water solubility. In all well-controlled studies reviewed that indicated daily intakes of more than 100 times the US recommended daily allowance of vitamin C, no adverse effects have been noted.\textsuperscript{80} Bendich and Langseth\textsuperscript{80} found that populations consuming more than 60 mg/d (US recommended daily allowance) of vitamin C from diet or supplements had a reduced risk of cancers, cardiovascular disease, and cataracts.

**VITAMIN E (α-TOCOPHEROL)**

Vitamin E includes tocopherols and tocotrienols and is present in vegetables, oils, seeds, corn, soy, whole wheat flour, margarine, nuts, some meats, and some dairy products. The alpha fraction performs the main physiologic activity of vitamin E, specifically, antioxidation; free d,α-tocopherol is the most biologically active form.\textsuperscript{125}

The membranes of tissue cells and intracellular organelles contain lipoprotein, consisting of a lipid portion that spontaneously oxidizes unless protected by antioxidants. In plasma and red blood cells, vitamin E is the main lipid-soluble antioxidant that protects cell membrane lipids from peroxidation and scavenges free radicals.\textsuperscript{126} When cell membrane peroxidation occurs, free radicals are released that destroy cells and cause enzyme expulsion, forming autoimmune antibodies and more cell destruction.\textsuperscript{127}

Vitamin E has been prescribed for most dermatologic conditions with conflicting results. To date, adequate controlled studies that clearly document a benefit from supplementation for most of these conditions have not been conducted.

**Photoprotection**

Topical application of antioxidants to animal skin, including α-tocopherol, has reduced sunburn cell production,\textsuperscript{117, 128} chronic UVB-induced damage,\textsuperscript{116, 129} and photocarcinogenesis.\textsuperscript{1} Oral and topical vitamin E reduce skin photoaging effects, skin cancer formation, and immunosuppression induced by UVR in animals.\textsuperscript{1, 130, 131, 132} Trevithick et
al found that topical d,α-tocopherol acetate reduced sunburn-associated erythema, edema, and skin sensitivity when applied to mice immediately after UVB exposure. Bissett et al found a 75% reduction of skin wrinkling, an increase in tumor latency, and a decrease of cutaneous tumors in mice with tocopherol 5% application before UVB exposure. UVA-induced skin sagging was not affected by tocopherol. In another study, tocopherol 5% to 8% cream applied to the face for 4 weeks decreased skin roughness, length of facial lines, and wrinkle depth when compared with placebo.

Werninghaus et al found that α-tocopherol had a photoprotective effect on cultured keratinocytes in humans compared with vehicle. Werninghaus et al conducted a randomized double-blind, placebo-controlled study of 12 patients to examine the photoprotective effect of 6 months of oral d,α-tocopherol acetate 400 IU daily on human skin. This supplementation did not significantly prevent or alter UV-induced skin damage in healthy individuals.

Inhibition of UV-induced erythema and edema with α-tocopherol supplementation in animals has not been clearly demonstrated in human skin. Vitamin E administration alone may not provide photoprotection, and some authors believe that other antioxidants (eg, ascorbic acid, selenium, or thiols) are necessary to prevent tocopherol’s degradation. Roles for vitamin E in photoprotection may be discovered in future double-blind controlled studies.

Skin cancer

Studies of vitamin E’s protection against skin cancers are contradictory. Gensler and Magdaleno found that, compared with placebo, topical vitamin E thrice weekly reduced skin cancer formation and prevented UV-induced immunosuppression in mice. Stryker et al evaluated dietary intake and plasma levels of retinoids, carotenoids, and vitamin E in 204 patients with melanoma and 248 control subjects and found no protection gained by increased plasma levels of these vitamins. Knekt found melanoma occurrence in patients inversely related to serum α-tocopherol levels. Serum vitamin E was 30% lower in 10 patients with melanoma and 5% lower in 35 patients with basal cell carcinomas, than in control subjects. He states that “this finding was not verified in another similar study and was contradicted in a case-control study, which reported a significantly lower vitamin E intake among melanoma patients but no differences in the serum levels between cancer patients and controls.” Wei et al, studying 131 patients with basal cell carcinoma and finding these
patients less likely than control subjects to have taken supplemental vitamins, concluded that regular vitamins A and E supplements were associated with a 70% reduced risk for basal cell carcinomas.

**Wound healing**

The effects of supplemental vitamin E on wound healing remains controversial. Parsa\textsuperscript{142} reviewed the literature and concluded that vitamin E, through its anti-inflammatory properties, may enhance wound healing. Lee\textsuperscript{143} conducted a randomized double-blind study in 57 patients with chronic gravitational ulcers, comparing vitamin E 400 mg/d to placebo. This was continued for 1 to 2 months after healing and reduced to 200 mg/d for 2 to 3 months without side effects. The condition of all patients healed within 3 to 4 months; 28 patients with stasis ulcers who were receiving oral vitamin E supplementation healed faster and more frequently than 29 patients receiving placebo. In a prospective, double-blind, randomized study, Jenkins et al\textsuperscript{144} found that topical vitamin E did not affect scar thickness or appearance. Local adverse reactions, including an epidemic of papular and follicular dermatitis, have been reported with topical use.\textsuperscript{144, 145}

**Immune function**

Vitamin E stabilizes lysosomes, interacts with eicosanoids to reduce prostaglandin $E_2$ synthesis,\textsuperscript{146} and increases IL-2 production, resulting in anti-inflammatory and immunostimulatory effects. Meydani et al\textsuperscript{132} studied immune responses of healthy adults with dl-$\alpha$-tocopherol acetate 800 mg/d for 30 days. The supplementation improved indices of cell-mediated immunity, enhancing mitogenesis, delayed-type hypersensitivity, and IL-2 formation. Studies of the elderly population indicate a lower incidence of infectious disease and cancer in those maintaining high plasma tocopherol levels.\textsuperscript{147, 148, 149}

**Dystrophic epidermolysis bullosa**

Case reports have illustrated successful treatment of dystrophic epidermolysis bullosa (DEB) with vitamin E,\textsuperscript{150, 151, 152, 153} and other studies have shown no effect.\textsuperscript{154, 155, 156} Michaelson et al\textsuperscript{157} described 3 patients with DEB whose condition responded to vitamin E, 200 to 600 IU daily. After 30 days of vitamin E therapy, previously increased collagenase activity in blister sites normalized. Some investigators\textsuperscript{158} believe collagenase is important in blister formation in DEB, and other
investigators\textsuperscript{159} consider increased local levels of collagenase to represent a secondary tissue reaction to chronic injury.

\textit{Discoid lupus erythematosus}

Burgess and Pritchard\textsuperscript{160} treated 25 patients with natural mixed tocopherol 600 mg/d, 24 of whom experienced improvement of the condition. Grubb and Hagerman\textsuperscript{161} found L-tocopherol 300 to 400 mg/d beneficial in 47 patients with superficial, recent-onset discoid lupus erythematosus. They believed the primary effect of vitamin E in discoid lupus erythematosus was collagen regeneration. Some authors\textsuperscript{162, 163} report improvement with vitamin E 1200 to 2000 mg/d without side effects, and other authors\textsuperscript{164, 165, 166, 167} report no effect with 300 to 600 mg/d.

\textit{Yellow nail syndrome}

Multiple case reports have documented the efficacy of vitamin E 800 to 1200 IU daily in yellow nail syndrome, a condition associated with lymphatic obstruction and pleural effusions.\textsuperscript{168, 169} The yellow pigment lipofuscin, derived from lipid precursors that undergo oxidation in tissue, may be responsible for yellow nail discoloration in this syndrome and in normal aging tissue.\textsuperscript{170} As oxidation continues, pigmentation is enhanced. Through antioxidation, vitamin E may block the pigment otherwise caused by oxidation products.\textsuperscript{168}

\textit{Granuloma annulare}

Cochrane\textsuperscript{171} reported 9 of 13 patients with granuloma annulare treated with vitamin E 300 IU daily were cured after approximately 7 weeks. Ayres and Mihan\textsuperscript{172} treated 12 patients with granuloma annulare with d,\textalpha-tocopherol acetate 300 to 1600 IU daily, and the condition of 6 patients cleared and of 5 patients improved. Topical vitamin E has cleared lesions in 1 to 3 weeks in many patients.\textsuperscript{173, 174}

\textit{Miscellaneous dermatologic conditions}

Fairris et al\textsuperscript{175} found no improvement in 60 patients with atopic dermatitis with vitamin E 600 IU daily. Ayres and Mihan\textsuperscript{176} reported 3 patients with benign familial pemphigus who responded to 800 to 1200 IU/d of d,\textalpha-tocopherol acetate; exacerbation occurred with a reduced dose and the disease abated with an increased dose. Ayres and Mihan\textsuperscript{177} described several patients with pseudo-xanthoma elasticum whose condition improved with supplemental vitamin E and recommended d,\textalpha-tocopherol
acetate or succinate 1200 to 1600 IU/d in early lesions. Ayres and Mihan treated 10 female patients with lichen sclerosus et atrophicus with d,α-tocopherol acetate 300 to 1200 IU/d and topical vitamin E. The condition of 5 patients markedly improved, of 2 patients moderately improved, and of 3 patients slightly improved. Several reports have demonstrated improvement of necrobiosis lipoidica diabetorum with oral vitamin E, starting with 100 IU/day. Ayres and Mihan treated 8 patients, each with scleroderma, morphea, or Raynaud’s phenomenon, with d,α-tocopherol acetate 800 to 1200 IU daily with good to excellent results. Wadleigh et al found that chemotherapy-induced oral mucositis resolved in 6 of 9 patients with topical vitamin E twice daily for 4 days as compared with no improvement in the placebo group.

**Dapsone-associated hemolysis**

Dapsone is an oxidative drug that produces met-hemoglobinemia and Heinz body hemolytic anemia at therapeutic doses. Antioxidants may counteract this effect. Kelly et al treated 17 patients with leprosy or dermatitis herpetiformis, taking dapsone 100 mg daily with supplemental vitamin E. When vitamin E 800 mg daily was added for 3 months, Heinz bodies were reduced with minimal effect on hemoglobin or reticulocyte counts.

Prussick et al studied the effects of daily oral vitamin C, vitamin E 800 IU/d, and both vitamins for 4 weeks, each administered to 15 patients being treated with dapsone for dermatitis herpetiformis. The hemoglobin concentration was higher; and the reticulocyte count, Heinz bodies, and methemoglobin concentration were lower when vitamin E was administered. The researchers concluded that this dose of oral vitamin E conferred a partial protective effect against dapsone-induced hemolysis. The use of vitamin E in patients receiving dapsone therapy is not recommended in common practice, and further studies in larger populations are needed to define a clinical relevance.

**Platelet aggregation**

Some studies show no change in platelet aggregation in individuals receiving supplements of vitamin E 800 to 1500 IU daily for 2 to 5 weeks, although Jandak et al demonstrated decreased platelet aggregation in normal individuals receiving supplements of vitamin E 200 to 400 IU daily for 2 weeks. Patients with abnormal platelets frequently responded with decreased platelet aggregation. Low vitamin E will inhibit platelet aggregation when combined with an arachidonic acid
inhibitor, such as aspirin, garlic, and curcumin.\textsuperscript{189}

Vitamin E has no measurable effect on coagulation in normal animals and humans; however, the administration of vitamin E to vitamin K–deficient animals and humans may enhance the coagulation defect.\textsuperscript{190} Whether to stop vitamin E before dermatologic surgery remains controversial. Patients with normal platelets who take vitamin E supplements probably have no clinically significant decrease in platelet aggregation, although it is recommended that patients with abnormal platelets or vitamin K deficiency or those taking antiplatelet agents stop vitamin E before surgery.\textsuperscript{191}

Safety

A review article\textsuperscript{192} in 1981 listed serious side effects of hypervitaminosis E: thrombophlebitis, pulmonary embolism, severe fatigue syndrome, gynecomastia, breast tumors, increased cholesterol and triglycerides, and altered immunity. Tsai et al\textsuperscript{193} found that megavitamin E supplementation does not affect general health but can cause a significant reduction of serum thyroid hormone and an increase in triglycerides. Subsequently, a series of controlled, double-blind studies and numerous anecdotal reports dispute the aforementioned adverse effects.\textsuperscript{177, 194} A comprehensive literature review\textsuperscript{195} in 1988 concluded that vitamin E is safe up to 3000 mg/d for prolonged periods. Kappus and Diplock\textsuperscript{194} concluded that daily vitamin E doses up to 400 mg are absolutely safe, that doses between 400 mg and 2000 mg are not likely to cause side effects, and that doses greater than 3000 mg daily over a long period may cause side effects.

Patients receiving anticoagulant therapy should avoid high doses of vitamin E (\textgreater{} 4000 IU) because vitamin E can enhance the anticoagulant effect.\textsuperscript{196} Vitamin E improves heart muscle tone and tissue glycogen storage. Patients with hypertension or insulin-dependent diabetes should start gradually with small doses, 100 IU/d, with blood pressure and glucose monitoring. d,α-Tocopherol acetate or succinate 1200 to 1600 IU daily without food is recommended.\textsuperscript{177} Inorganic iron, derived from enriched white bread, frequent laxative use, and female hormones (ie, oral contraceptives) antagonizes vitamin E, which is not approved for the treatment of dermatoses in North America.

SYNERGISTIC EFFECTS OF VITAMINS A AND E

Ames\textsuperscript{197} described synergism between vitamins A and E by demonstrating that rats receiving a vitamin E–deficient diet experienced the development of a low vitamin A level that persisted despite oral and parenteral vitamin A
supplementation and that was normalized with dietary vitamin E. Many
dermatologic conditions have been treated with vitamins A and E
concomitantly, although reports are anecdotal and randomized; double-
blind trials are necessary.

*Acne vulgaris*

Defective keratinization may be corrected by the synergism of vitamins A
and E. Through antioxidation, vitamin E controls inflammation caused by
peroxidation of lipids released from ruptured follicle walls that contact
oxygen in the tissues.\textsuperscript{198} Ayres and Mihan\textsuperscript{198} treated 98 patients with acne
vulgaris with vitamins A and E 100,000 IU/d and 800 IU/d, respectively,
without undesirable side effects. They reported good to excellent results in
90% of patients in 6 to 8 weeks and continued the regimen for several
months with a low maintenance dose for several years.

*Keratosis follicularis (Darier’s disease)*

Ayres and Mihan\textsuperscript{199} successfully treated Darier’s disease with vitamins A
and E in patients unresponsive to large doses of vitamin A. Ayres and
Mihan\textsuperscript{199} reported a patient with Darier’s disease for 13 years,
unresponsive to vitamin A 200,000 IU/d for 5 years. When vitamin A was
decreased to 100,000 IU/d and vitamin E 1600 IU/d was added, the
eruption resolved in months without recurrence after years.

*Pityriasis rubra pilaris*

Ayres and Mihan\textsuperscript{198} reported 4 patients with pityriasis rubra pilaris whose
condition cleared in months with vitamin A 20,000 to 100,000 IU/d and
vitamin E 200 to 1600 IU/d. The condition of these patients remained
under good control after years, without adverse effects.

*Ichthyosis*

Ichthyosis has been treated successfully with vitamin A 100,000 IU/d and
vitamin E 800 to 1600 IU/d in patients whose condition was previously
unresponsive to vitamin A alone, without adverse effects.\textsuperscript{200}

**CONCLUSION**

Vitamins A, C, and E and related compounds are useful therapeutic agents
in the prevention and treatment of photoaging, skin cancer, and numerous
skin disorders. Through antioxidation, these vitamins protect living cells
from damage initiated by free radicals. The authors reviewed selected articles from the literature to encourage and stimulate further interest and investigation into the usefulness of these agents. Future studies may elucidate specific roles and mechanism of action of antioxidant vitamins in dermatologic health and disease.

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