Nutritional skin care: health effects of micronutrients and fatty acids[1–3]

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ABSTRACT Human skin is continuously exposed to internal and external influences that may alter its condition and functioning. As a consequence, the skin may undergo alterations leading to photoaging, inflammation, immune dysfunction, imbalanced epidermal homeostasis, or other skin disorders. Modern nutritional science is developing new insights into the relation between food intake and health, and effects of food ingredients may prove to be biologically relevant for optimal skin condition. The objective of this review was to evaluate the present knowledge about the interrelation of nutrients and skin, particularly the photoprotective effects of nutrients, the influences of nutrients on cutaneous immune responses, and the therapeutic actions of nutrients in skin disorders. The nutrients of focus were vitamins, carotenoids, and polyunsaturated fatty acids. Supplementation with these nutrients was shown to provide protection against ultraviolet light, although the sun-protection factor was relatively small compared with that of topical sunscreens. An increase in delayed-type hypersensitivity skin responses after supplementation with nutrients has proven beneficial, especially in elderly people, and may boost cell-mediated immunity. Dietary consumption of certain plants or fish oil is known to modulate the balance of lipid inflammatory mediators and, therefore, is valuable in the treatment of inflammatory skin disorders. It was concluded that nutritional factors exert promising actions on the skin, but information on the effects of low-to-moderate doses of nutrients consumed long term by healthy individuals is obviously lacking, as are data on direct effects on basal skin properties, including hydration, sebum production, and elasticity. *Am J Clin Nutr* 2001;73:853–64.

INTRODUCTION

Human skin acts as a barrier between the internal and external environments, protecting the body from mechanical damage, noxious substances, invasion by microorganisms, and radiation. The skin plays an important role in regulating body homeostasis by keeping water loss to a minimum and by regulating body temperature. Moreover, the skin lodges nerve endings that react to pain and temperature. In recent years it has become clear that the skin is an essential part of the immune system (1). Besides these vital biological functions, the skin plays a pivotal role in the feeling of well-being and in physical attractiveness. Appearance of the skin is primarily determined by its surface texture, color, and physiologic properties such as elasticity, sweat, scent, and sebum production. Skin condition and functioning are affected by environmental factors, such as ultraviolet (UV) irradiation, free radicals, toxic and allergic compounds, and mechanical damage, and by endogenous factors, such as genetic predisposition, immune and hormone status, and stress. Consequently, the skin undergoes alterations resulting in photoaging, inflammation, reduced immune function, imbalanced epidermal homeostasis, and other skin disorders (2, 3).

Skin functioning and skin attractiveness are dependent on nutrition. This is evidenced by the development of skin lesions in response to nutritional deficiencies. Dietary supplementation with the deficient vitamins, minerals, or essential fatty acids improves skin conditions in these situations (4).

Modern nutritional science is now developing new insights into the relation between food intake and health, and interest in the role of diet, specific food ingredients, and supplements in reducing the risk of skin disorders is growing. Specific positive effects of food ingredients on skin conditions may prove to be biologically relevant and may consequently allow for claims on products containing these functional ingredients, resulting in the development of new functional foods for optimal skin condition.

In this review, published data from MEDLINE (National Library of Medicine, Bethesda, MD) and CURRENT CONTENTS (Institute for Scientific Information, Philadelphia) dated from 1980 on the interrelations of nutrients and human skin are summarized and critically evaluated. Only articles written in English were included and studies of skin carcinogenesis were excluded. The results of this review may provide a basis for the feasibility of the concept of functional foods for optimizing skin conditions and preventing skin disorders. Studies were roughly categorized into those that addressed the photoprotective effects of

nutrients, the effects of nutrients on cutaneous immune responses, and the therapeutic actions of nutrients in skin disorders. This review is not exhaustive, but does include the most important studies that showed associations between nutrients and human skin.

PHOTOPROTECTIVE POTENTIAL OF VITAMINS, CAROTENOIDS, AND POLYUNSATURATED FATTY ACIDS

Sunburn is a well-known acute effect of excessive sun exposure. Low-dose or short exposure to UV irradiation is tolerated by the skin without noticeable or clinically relevant changes. Only after a certain threshold is reached does delayed and prolonged vasodilatation develop, allowing passage of lymphocytes and macrophages into the tissue and induction of an inflammatory response that is clinically visible as erythema. A frequently used measure of UV irradiation–induced erythema is determination of the minimal erythema dose (MED). One MED is the minimal amount of energy required to induce a uniform, clearly demarcated redness 16–24 h after exposure to UV irradiation.

The ultimate aim of efforts to protect the skin against sunlight is prevention of photoaging (5), photoimmunosuppression (6), and photocarcinogenesis (7). Although nature anticipates these conditions by increasing epidermal thickness, stimulating melanogenesis, and providing natural antioxidants in the superficial skin layers, supplementation with nutrients may support these processes and thereby serve as an additional protective measure against the harmful effects of UV light.

Vitamins E and C

During the past 2 decades, only 4 clinical studies investigated the photoprotective effects on skin of dietary supplementation with vitamins C and E. In a double-blind, parallel, placebo-controlled trial, La Ruche and Cesarini (8) investigated the photoprotective effects of vitamins and trace elements. Sixteen healthy volunteers received 200 µg Se, 16 mg copper sulfate, 14 mg α-tocopherol, and 2700 µg retinol; only trace elements (200 µg Se and 16 mg copper sulfate); only vitamins (14 mg α-tocopherol and 2700 µg retinol); or placebo for 3 wk. All treatments with active ingredients provided partial protection against the formation of sunburn cells at a low irradiation dose (suberythemal) compared with the placebo group. Sunburn cells are characteristic keratinocytes with a glossy, shrunken eosinophilic cytoplasm and a pyknotic nucleus that appear in the epidermis after UV irradiation and may be used as a sensitive marker of UV irradiation–induced injury. Supplementation with either trace elements or vitamins resulted in a lower number of sunburn cells after irradiation, whereas supplementation with both trace elements and vitamins resulted in an additional reduction in the number of sunburn cells. No effects on the MED were shown, although effects may have been missed because of the small number of subjects in each group or the low doses of antioxidants in the supplement. The absence of effects in the supraerythemal dose may be explained by the increase in cell death at higher doses of UV irradiation, at the cost of a reduction in the number of sunburn cells. Although this study showed a protective effect of trace minerals and vitamins at low irradiation doses, with the formation of sunburn cells as a biological endpoint, no effects were shown on UV light–induced erythema.

In a study by Werninghaus et al (9), a relatively small group of 12 healthy volunteers received 295 mg (400 IU) α-tocopherol acetate or a placebo daily for 6 mo along with their regular diet. Mean MEDs were similar in both groups before supplementation, but increased in some subjects and decreased in others after supplementation. Plasma concentrations of α-tocopherol increased during the study, but no parallel increase was detected in the skin. This finding was explained by the fact that the skin samples were taken 24 h after exposure and thus α-tocopherol may have been depleted from the skin. Moreover, the study spanned several months and because individual MEDs were shown to be higher in summer than in winter (10), seasonal changes may have obscured any effects. In contrast with the findings of La Ruche and Cesarini (8), no change in the number of sunburn cells was found in the subjects who received the supplement. A major reason for this lack of an effect may have been that manipulation of vitamin E concentrations only may be inadequate to provide photoprotection because other antioxidants have been shown to be of critical importance in the recycling of UV irradiation–induced α-tocopherol radicals (11).

In another study, much higher doses of 2 g α-tocopherol/d, 3 g ascorbate/d, a combination of both vitamins, or a placebo were administered to 40 healthy volunteers for 50 d (12). Bioavailability was established by the increased concentrations of α-tocopherol and ascorbate in buccal mucosal keratinocytes after supplementation. MEDs increased markedly after intake of the combination of α-tocopherol and ascorbate. Obviously, because MEDs also increased slightly in subjects who received either vitamin alone or placebo, seasonal influences may have interfered with the measurements. Nevertheless, the interaction between vitamins E and C likely explained their more pronounced photoprotective effect compared with that of either vitamin alone. Although this study convincingly showed that vitamin supplementation effectively protects the skin against sunburn, the doses of vitamins used were much higher than amounts generally ingested from habitual diets.

The protective effect of a combination of vitamins E and C was also shown by Eberlein-König et al (13). In this study, subjects received lower dosages of 671 mg vitamin E/d and 2 g vitamin C/d for a relatively short time, 8 d. Despite these lower dosages, mean MEDs increased compared with baseline in 8 of 10 subjects receiving the supplement. In the placebo group the MED was unchanged in 6 of 10 subjects but, remarkably, decreased in 4 subjects. The authors suggested that the initial UV irradiation–induced erythema may have temporarily primed the adjacent tissue to respond more intensively to a second irradiation. After the 8-d supplementation with vitamins E and C, exposure of the skin to UV irradiation also resulted in decreased cutaneous blood flow, whereas it increased in the placebo group. It was concluded that short-term supplementation with moderately high doses of vitamin E and C exerts a photoprotective effect.

Carotenoids

Of all the carotenoids, β-carotene has been the focus of most attention because it makes the most important quantitative contribution to human nutrition. At least one other carotenoid, lycopene, has been detected in the skin (14, 15). Since 1980, 8 studies have assessed the photoprotective potential of β-carotene supplementation.

In a study by Wolf et al (16), 23 healthy volunteers received 150 mg of an oral carotenoid preparation containing 60 mg β-carotene and 90 mg canthaxanthin daily for 4 wk. No differences

in MEDs were shown in a comparison of values before and after carotenoid supplementation. Concentrations in serum increased during treatment, but concentrations in the skin were not reported. Additionally, no effects of β-carotene were detected when UV irradiation–induced unscheduled DNA synthesis was investigated, suggesting that carotenoids were not protective against DNA lesions repairable by excision repair. The authors concluded that oral carotenoids were not photoprotective.

An extensive study was performed a few years later by Garmyn et al (17). In this study, 16 healthy women underwent dietary restriction for 3 wk to reduce plasma baseline β-carotene to low-normal concentrations. Five days after ingestion of a single dose of 120 mg β-carotene, there was no significant change in the intensity of erythema after a constant dose of UV radiation. Moreover, an intake of 90 mg β-carotene/d for 23 d in conjunction with the habitual diet did not change the intensity of erythema. Although β-carotene concentrations increased in both plasma and skin under both conditions, there were no effects of supplementation on biological features, eg, the number of sunburn cells and clinical appearances (intensity of erythema after acute exposure to sunlight).

In contrast, intake of a much lower dosage of β-carotene (30 mg/d) for 10 wk increased the yellow component of the skin at all body skin sites, as measured by chromametry, although this color change was not visible (18). After the 10-wk supplementation period, supplementation continued in conjunction with exposure to natural sunlight for 13 d, ie, approximately equivalent to a 2-wk vacation in the sun. During this period, the development of erythema in subjects who had taken β-carotene was much less pronounced than in the placebo group. During sun exposure, serum β-carotene concentrations decreased to subphysiologic concentrations in the placebo group. Such low concentrations are possibly associated with an increased cancer risk. In the supplemented group, however, concentrations did not fall below reference values during sun exposure. Gollnick et al (18) concluded that presupplementation with moderate dosages of β-carotene (30 mg/d) before and during sunlight exposure provides protection against sunburn, possibly because of the increased absorption capacity of the skin or because β-carotene concentrations in the skin do not decrease to below concentrations considered to be critical. The study also showed that the combination of systemic and topical photoprotection by sunscreens offers a synergistic effect.

The beneficial effects of a combination of β-carotene and other antioxidants was investigated by Postaire et al (19). In this study, 10 subjects received a supplement providing 13 mg β-carotene, 2 mg lycopene, 5 mg tocopherol, and 30 mg ascorbic acid daily for 8 wk. This lower dosage of β-carotene than that received by Gollnick et al's (18) subjects also resulted in an increase in the yellow component of the skin as measured by chromametry. In contrast, 10 subjects who ingested a similar supplement containing only 3 mg β-carotene and 3 mg lycopene showed no skin discoloration. On the basis of these changes in skin color, Postaire et al concluded that β-carotene concentrations increased after 8 wk in the skin of the subjects who ingested 13 mg β-carotene and that melanin concentrations increased after 4 wk in both groups. Because photoprotection was not measured in that study, the authors could only speculate about the role of carotenoid supplementation and hence suggested that carotenoids may be photoprotective partly because they stimulate melanogenesis.

An increase in the yellow component of the skin was also shown in 12 subjects whose habitual diet was supplemented with 50 mg of a natural carotenoid mix daily for 6 wk (20). Parallel with this increase in the yellow component of the skin, the degree of redness in the skin after exposure to constant UV irradiation decreased as supplementation progressed. Moreover, on the basis of alterations in skin color, carotenoid concentrations in the skin increased. UV irradiation for 6 wk resulted in a lower increase in hemoglobin, suggesting that UV irradiation–induced vasodilatation was much less pronounced, likely as a result of β-carotene supplementation. However, because no interindividual variations were presented, only trends could be interpreted. Nevertheless, the authors suggested that carotenoid supplementation increased the reflection capacity of the skin, thereby improving its protective function.

In a recent study by Stahl et al (21), 20 healthy subjects received 25 mg of a natural carotenoid mix (23.8 mg β-carotene, 0.75 mg α-carotene, 0.18 mg cryptoxanthin, 0.15 mg zeaxanthin, and 0.12 mg lutein) daily or a combination of this mix and 335 mg α-tocopherol. After supplementation for 12 wk, both groups showed a slight yellowing of the skin and elevated concentrations of β-carotene in both serum and skin. The mean degree of erythema after exposure to UV irradiation was lower 8 wk after supplementation than it was before supplementation. Because the degree of erythema was lowest in the group who received the carotenoid mix plus α-tocopherol, the authors suggested that vitamin E may provide a higher level of protection against UV irradiation–induced erythema than do carotenoids alone.

A comparable supplement, providing 30 mg of a natural carotenoid mix (29.4 mg β-carotene, 0.36 mg α-carotene, 0.084 mg cryptoxanthin, 0.072 mg zeaxanthin, and 0.054 mg lutein) daily was provided to 22 subjects for 8 wk in a trial by Lee et al (22). The concentration of carotenoids was enhanced at 30-mg increments every 8 wk to a final dose of 90 mg/d. Supplementation with 60 and 90 mg carotenoids/d resulted in a dose-dependent increase in MEDs. Moreover, serum β-carotene concentrations increased after each subsequent supplementation; however, concentrations in the skin were not presented. The authors also showed that the 2 highest concentrations of the carotenoid mix inhibited serum lipid peroxidation. It was concluded that the dose of sunlight required to produce a minimal perceptible erythema increased with increasing doses of carotenoids.

n−3 Polyunsaturated fatty acids

In the search for means to improve human health, n−3 polyunsaturated fatty acids (PUFAs) have been promoted as valuable dietary compounds. Common food sources of n−3 PUFAs are cod liver oil, fish oil, and marine animals with a high amount of fat, such as mackerel, salmon, and menhaden. Many reports suggest that the intake of n−3 PUFAs, particularly eicosapentaenoic acid (EPA; 20:5n−3), may provide considerable health benefits in relation to inflammatory diseases. Since 1980, 4 studies have assessed the photoprotective effects of dietary intakes of fish oil.

In a study by Orengo et al (23), 10 subjects enriched their diets daily with fish oil containing 2.8 g EPA and 1.2 g docosahexaenoic acid (DHA; 22:6n−3) and 10 other subjects received a placebo. After 4 wk, a small but statistically significant increase in the MED was seen in the fish-oil group, which corresponded to a sun-protection factor slightly >1. Fish-oil supplementation did not change prostaglandin E_2 (PGE_2) concentrations significantly.

This study showed that at a relatively low dose (2.8 g EPA and 1.2 g DHA) of fish oil and within a short period of time, consumption of n−3 PUFAs was photoprotective.

Dietary supplementation of 15 subjects with 10 g fish oil/d, which provided 18% EPA and 12% DHA, resulted in an increase in the MED after 6 mo (24); 10 wk after fish-oil supplementation ended, the MED decreased again. However, parallel to an increase in total n−3 fatty acids in the epidermis, lipid peroxidation products increased in irradiated skin. Although fish-oil consumption reduced UV irradiation–induced erythema, the susceptibility of the skin to lipid peroxidation increased because of the unstable nature of n−3 fatty acids.

In a follow-up study (25), dietary supplementation of 16 individuals with a similar amount of fish oil (10 g/d) resulted in an increase in the MED after only 3 mo. PGE_2 concentrations in skin fluid collected by the suction blister fluid method decreased after fish-oil consumption both in nonirradiated and irradiated skin. The authors suggested that the reduced responsiveness to UV irradiation–induced erythema after long-term supplementation with fish oil may have been due, at least in part, to the inhibition of PGE_2 concentrations in the skin.

In a recent study, the protective role of dietary EPA supplementation against the acute effects of a single dose of UVB irradiation was investigated. Twenty-eight subjects received 4 g 98% EPA or 98% oleic acid daily for 3 mo (26). In the EPA-supplemented group, UVB irradiation–induced erythema and p53 induction decreased, whereas no significant changes were found in the oleic acid group. Hence, dietary supplementation with EPA was shown to protect the skin both at the macroscopic and cellular levels, despite an increase in oxidative stress.

Conclusion

In conclusion, supplementation of the habitual diet with vitamins, carotenoids, PUFAs, or a combination thereof may protect the whole body against UV irradiation–induced damage. In contrast, topical sunscreens act only locally and have to be applied regularly. Although the additive effect of dietary supplementation with vitamins, carotenoids, PUFAs, or a combination thereof may be small, fair-skinned individuals particularly may benefit from this type of protection. Nevertheless, intakes well above those usually encountered in the diet are necessary to achieve such a photoprotective effect and the sun-protection factor of this approach is much lower than that expected from the use of topical sunscreens. Little is known about the photoprotective effects of vitamin, carotenoid, or PUFA intakes when consumed at "nutritional" amounts over the long term, but this issue may be of interest in the development of functional foods. With regard to the bioavailability of vitamin E in the skin after oral intake, Fuchs and Kern (12) showed the presence of this vitamin in mucosa-derived keratinocytes 50 d after supplementation. Significant correlations were shown between concentrations of α-tocopherol in plasma and in buccal mucosal cells and skin samples (27). Just the presence of this vitamin in the skin does not imply a photoprotective role. The observation that supplementation with vitamin E alone did not protect against sunburn (9) is likely explained by the fact that UV irradiation exposure was shown previously to deplete vitamin E in the skin as a result of oxidation (28). Vitamin E radicals have to be regenerated by other antioxidants, eg, vitamin C, and this recycling function presumably contributes to the synergistic action of antioxidants and the lack of effect when only a single antioxidant is provided (29). Although La Ruche

and Cesarini (8) showed no photoprotective effect of a combination of vitamins and trace elements, the lack of effect may have been due to the relatively low doses of vitamin E (14 mg) administered relative to the doses used in other studies (12, 13).

In addition, MEDs were shown previously to vary considerably between individuals, indicating that sufficiently large groups are necessary in a study to detect any consistent effects (10). The number of subjects in the study of La Ruche and Cesarini (8) and of Werninghaus et al (9) may have been too small.

Besides its antioxidative properties, vitamin E was shown to modulate arachidonic acid metabolism (30). The interaction of vitamin E with the eicosanoid system may result in an antiinflammatory effect and thereby complement the photoprotective effects of other antioxidants in the skin.

Although some carotenoids can act as vitamin A precursors, other biological activities may be just as interesting, such as their potential to alter absorption characteristics of the skin, antioxidant function, and immunomodulatory effects. Although the efficiency of carotenoid absorption is relatively low, moderate intakes of carotenoids were shown to induce a change in skin color. β-Carotene was detected in the skin after both single and repeated oral supplementation (31, 32). Analysis of reflection spectra of the skin showed that the increase in carotenoids varied, depending on the body site, from 0.7-fold in dorsal skin to 17-fold in the back of the hand after consumption of 25 mg total carotenoids for 12 wk (33). Also, several other studies showed that consumption of β-carotene induced an increase in the reflective properties of the skin (18–20). Although the amounts of carotenoids deposited in the skin were shown to be insufficient to act as a physical sunscreen (34), β-carotene may have a direct photoprotective effect because of its physical ability to absorb light.

Carotenoids were shown previously to be efficient quenchers of singlet oxygen and to scavenge free radicals (35) and these antioxidant functions may be responsible for their protective effect. Lycopene was reported to have a singlet oxygen quenching ability better than that of β-carotene (36). Ribaya-Mercado et al (15) showed that lycopene was present in the skin in concentrations similar to those of β-carotene and that exposure of the skin to UV light decreased skin lycopene concentrations more so than skin β-carotene concentrations. Biesalski et al (31) reported that during UV irradiation, plasma β-carotene concentrations decreased in subjects who received a placebo but did not change in subjects who received β-carotene; plasma lycopene concentrations remained constant in both groups. Skin β-carotene concentrations decreased slightly after UV irradiation; however, skin lycopene concentrations were not provided. In Biesalski et al's study (31), the subjects' skin was exposed to sunlight for 12 d, whereas in Ribaya-Mercado et al's study (15), the subjects' skin was exposed to UV light only once. This difference may explain the apparent differences in findings between the studies. Thus, although most studies focused on the effects of β-carotene, it is likely that other carotenoids, such as lycopene, act synergistically with β-carotene to protect the skin from UV irradiation.

The most important benefit of oral n−3 PUFA intakes from fish oil may be ascribed to their antiinflammatory effects. These effects of n−3 PUFAs have been reported to be the result of their competition with n−6 PUFAs as a substrate for cyclooxygenase and lipoxygenase, resulting in the formation of less active prostaglandins and leukotrienes (37). Interference with inflammatory cascades in the skin may occur through reductions in the synthesis of proinflammatory lipid mediators, such

as leukotriene B_4 (LTB_4) and PGE_2 (25, 38), or through reductions in the production of cytokines, such as interleukin 1 and tumor necrosis factor α (39).

Moreover, n−3 PUFAs are unstable and may preferably be damaged by free radicals, thereby protecting other structures from attack by free radicals. Nevertheless, to protect against excessive formation of free radicals and lipid peroxidation, appropriate amounts of antioxidants (eg, vitamin E) should also be consumed. The ability of vitamin C, vitamin E, and carotenoids to influence the damaging effects of UV light may be mediated largely by their antioxidant function, but it is likely that other biological activities are involved that are not yet completely clear.

ENHANCEMENT OF CUTANEOUS IMMUNE RESPONSE BY VITAMINS, CAROTENOIDS, AND POLYUNSATURATED FATTY ACIDS

In addition to the acute effects of UV light with respect to sunburn, chronic sun exposure and aging are associated with decreased humoral and cell-mediated immune responses (40). Because immune function is known to decline with age and because elderly people often have a high prevalence of vitamin deficiencies, the suggestion was raised that this subclinical malnutrition may contribute to decreased immune function (41). Research in this area has focused mainly on elderly individuals to investigate the possibility that normal immune function can be restored or maintained by supplementation with micronutrients.

Delayed-type hypersensitivity (DTH) skin tests with a panel of antigens have generally been accepted as an important means of monitoring the status of cell-mediated immunity in vivo (42). DTH skin responses can be quantitated by measuring the number and diameter of the reddened area that appears at the site of topical application of a series of commonly encountered antigens.

Vitamins

The growing attention to health maintenance has been accompanied by an increased use of vitamin and mineral supplements by healthy individuals. Goodwin and Garry (43) studied the immunologic effects of megadoses of vitamin and mineral supplements, ie, intakes >5 times the recommended dietary allowance (44), in healthy elderly individuals aged >65 y. The subjects were divided into those in the top 25% or top 10% of total intake for specific nutrients and were compared with the subjects in the bottom 75%. Only subjects who ingested megadoses of vitamin C showed a trend for increased skin test reactivity. Other indicators of immune function were not significantly different between the group who took megadoses of vitamin and mineral supplements and those who did not. In a later study by the same authors, a large group of 230 healthy subjects aged 65–94 y was evaluated (45). Except for stronger DTH skin responses in subjects with low folic acid concentrations, no significant differences in immune responses were found in comparisons of individuals with low and high blood micronutrient concentrations. Thus, Goodwin and Garry concluded that subtle nutritional deficiencies are not likely associated with the depressed immune function observed in healthy elderly individuals.

In many studies by Bogden et al (46–49), the effects of zinc and vitamins were investigated in elderly individuals. In one study these investigators showed that plasma zinc concentrations were positively associated with the response to skin-test antigens and therefore suggested a role for systemic zinc in DTH skin

responses (46). However, administration of zinc (15 and 100 mg/d) or placebo for 3 mo to 103 elderly subjects did not alter skin responses to a panel of antigens (47). Bogden et al concluded that pharmacologic doses of zinc do not affect cellular immune function, but they did not exclude the possibility of a possible beneficial effect in specific subgroups of elderly or the possibility that longer periods of supplementation are necessary to adequately define the effects of zinc on immune function. Therefore, a 1-y study was conducted in which elderly subjects received a "one-a-day" type multivitamin-mineral supplement (containing amounts near the recommended dietary allowance of essential micronutrients) with (15 or 100 mg Zn/d) or without zinc (48). DTH skin responses increased after intake of the multivitamin-mineral supplement, but, surprisingly, decreased and were delayed in subjects who ingested 15 or 100 mg Zn. In contrast, another measure of cellular immune function, ie, natural killer cell activity, was enhanced in the subjects who ingested the highest dose of zinc. It was concluded that the presence of zinc possibly interfered with the absorption or metabolism of one or more nutrients in the multivitamin supplement, thereby inhibiting optimal uptake of the supplement. In a follow-up of this study, Bogden et al (49) focused mainly on the immune-enhancing effects of multivitamin-mineral supplements. They studied the effects of an over-the-counter supplement (containing 15 mg Zn) in 29 elderly subjects aged 59–85 y. The number of positive responses and induration increased from baseline after 12 mo of supplementation. No changes in DTH skin reactivity occurred in the placebo group. The authors indicated that β-carotene, folate, vitamin E, and, particularly, vitamin C were the most important nutrients for modulating skin reactivity. No further reference was made to the influence of zinc.

The effect of supplementation with vitamin E alone on immune function was investigated in a study by Meydani et al (50). Elderly subjects aged >60 y received either 800 mg α-tocopheryl acetate or a placebo daily for 30 d. DTH skin responses increased in the supplemented group, whereas no change was observed in the placebo group. Because PGE_2 formation decreased in activated peripheral blood monocytes after supplementation with vitamin E, it was suggested that its immunostimulatory role may have been due to its ability to decrease PGE_2 production and, possibly, lipid peroxidation products. The high dosage of α-tocopheryl acetate (800 mg/d) used by Meydani et al may explain the more rapid alterations in DTH skin responses that they observed than did Bogden et al (46), who used a dose of 22 mg.

In a follow-up to their original study (50), Meydani et al (51) administered dosages of 60, 200, and 800 mg vitamin E/d to elderly subjects aged >65 y for a much longer time, 235 d. All 3 supplemented groups showed an increase in DTH skin responses after 128 d of treatment compared with baseline; the greatest increase was in the group who received 200 mg vitamin E/d. Besides the beneficial effect of short-term supplementation with megadoses of vitamin E (800 mg/d), as was shown in their original study (50), Meydani et al (51) showed that lower doses (60 and 200 mg/d) consumed for a longer period of time increased cell-mediated immunity in the elderly. However, it was suggested that there might be a threshold level for the immunostimulatory effects of vitamin E.

Pallast et al (52) administered 100 or 50 mg α-tocopherol acetate or a placebo to elderly individuals aged 65–80 y. After 6 mo of supplementation, only the group who received 100 mg vitamin E showed an increase from baseline in the number of

positive DTH skin reactions, especially those who were physically less active or who had low DTH skin reactivity at baseline. Surprisingly, the overall DTH score increased in all 3 groups, which was explained by the existence of a placebo or seasonal effect or by the coincidental increase in vitamin C concentrations during the intervention. Nevertheless, it was concluded that subjects with the highest risk of mortality, ie, those with low DTH skin responses and low physical activity, may benefit most from vitamin supplementation.

To further support the beneficial effects of vitamins on immune function, Jacob et al (53) used an opposite study design in which 12 individuals aged 25–43 y were depleted of vitamin C for 32 d and then received either 10 or 20 mg vitamin C/d for 28 d and either 60 or 250 mg vitamin C/d for the following 28 d. Plasma vitamin C concentrations and DTH skin responses decreased during the depletion period and, although plasma vitamin C concentrations increased in the repletion period, DTH skin responses did not return to predepletion concentrations. Thus, these investigators showed that conditions of moderate vitamin deficiency reduce cell-mediated immunity and oxidative defense.

Bunker et al (54) performed a study in which housebound elderly subjects aged 70–85 y were given a commercially available high-protein milk drink containing moderate amounts of a large number of vitamins and macronutrients and a capsule containing a mixture of trace elements for 12 wk. Minimal increases in DTH skin responses were found in the supplemented group, but skin reactivity also increased in the placebo group. An interesting point was made in this study: namely, that the increase in cell-mediated immunity in both the placebo and treatment groups possibly was the result of decreased physiologic stress during the study because of less social isolation. That is, improvements in well-being may have in turn improved immune function. Furthermore, the doses may have been too low and the time period too short to detect any effect of nutrients in the supplemented individuals.

To determine the effects of long-term daily supplementation with vitamins and trace elements, a large study was performed by Girodon et al (55). A large group of 725 institutionalized elderly subjects with a mean age of 84 y received either trace elements (20 mg Zn and 100 μg Se), vitamins (120 mg ascorbic acid, 6 mg β-carotene, and 15 mg α-tocopherol), a combination of trace elements and vitamins, or a placebo for 2 y. Supplementation with low doses of vitamins and trace elements normalized their serum concentrations, thereby correcting specific nutrient deficiencies. Nevertheless, DTH skin reactivity was not influenced and even decreased after 6 and 12 mo of supplementation. This may be explained by the fact that the study population consisted of institutionalized elderly patients who had a suboptimal health status. The results of this study are in obvious contrast with those of the study by Bogden et al (49), in which a low-dose multivitamin supplement improved DTH skin reactivity. The authors suggested that differences in the populations accounted for the obvious contrasts between the studies, even though the results of Pallast et al (52) indicated that the subjects with the highest risk of mortality would particularly benefit from supplementation.

Carotenoids

It is generally accepted that exposure to UV light suppresses immune function. Carotenoids have been shown to provide moderate protection against sunburn; however, only 2 studies performed in the past 2 decades investigated the potential of β-carotene to protect against UV light–induced immunosuppression.

Fuller et al (56) studied the effects of supplementation with either 30 mg β-carotene or a placebo daily in 24 men aged 19–39 y who ingested the supplement with a single-menu, low-carotenoid diet for 70 d. From day 28, the subjects were exposed to UV light 12 times over 16 d. No reductions in plasma carotenoid concentrations were observed in either group. DTH skin responses decreased in the placebo group but remained unchanged in the supplemented group. It was concluded that β-carotene protected against photosuppression of the immune system in the young healthy men and that β-carotene supplementation may be beneficial in those with compromised immune function.

A similar study was performed by Herraiz et al (57). In this study, 32 elderly men aged 55–79 y received either 30 mg β-carotene or a placebo daily with a low-carotenoid diet for 47 d. Repeated exposure to UV light resulted in a decrease in DTH skin responses in the placebo group but not in the supplemented group, whereas plasma β-carotene concentrations were not affected. Higher plasma β-carotene concentrations were associated with higher resistance to immunosuppression after exposure to UV light. The overall effects were less pronounced in the elderly men than in the younger men, which was suggested to be due to lower plasma β-carotene responsiveness and higher variability in skin reactivity in the elderly subjects.

Polyunsaturated fatty acids

Dietary fatty acids have been shown to be capable of changing the fatty acid composition of membrane phospholipids of immune cells, thereby modulating the function of these cells. Consequently, the production of eicosanoids may be influenced as well as the activity of membrane-associated enzymes. Since 1980, few studies of the effects of PUFAs on DTH skin responses have been published.

In a study by Kelley et al (58), the effects of dietary n−3 PUFAs on several indexes of immune status were investigated in 10 healthy men who consumed a diet enriched with flaxseed oil containing 21% α-linolenic acid (18:3n−3) compared with 1% α-linolenic acid in the control diet. The flaxseed oil tended to decrease DTH skin reactivity. Although the number of subjects in this study may have been too small, in vitro measures of cell-mediated immunity showed a significant suppressive effect of flaxseed oil. Suppression of cell-mediated immunity by flaxseed oil may not be desirable in healthy individuals but may be useful in the treatment of autoimmune diseases or inflammatory conditions.

The effects of a salmon-containing diet on immune status were assessed in 9 healthy men aged 30–65 y (59). Daily consumption of 500 g salmon containing 2.3 g EPA and 3.6 g DHA for 40 d did not significantly affect DTH skin reactivity. This study showed that moderate consumption of n−3 fatty acids does not suppress the immune system.

Wu et al (60) investigated the effects in 20 elderly subjects aged ≥65 y of the consumption for 2 mo of black currant seed oil containing 63 mg γ-linolenic acid (18:3n−6) or a placebo. In the group that consumed black currant seed oil, plasma concentrations of γ-linolenic acid, α-linolenic acid, and dihomo-γ-linolenic acid (20:3n− 6) increased and arachidonic acid concentrations were unchanged, whereas no changes in any fatty acid occurred in the placebo group. DTH skin responses to only one antigen were significantly different from presupplementation

values and from those of the placebo group. Furthermore, there was a decrease in PGE_2 production by polymorphonuclear leukocytes. Hence, the modest immunomodulating effects of black currant seed oil were suggested to result, in part, from a reduction in the inflammatory mediator PGE_2.

Conclusion

Although no agreement exists regarding the exact changes in the individual components of the immune system with aging, depression of T cell–mediated function appears most susceptible to immunosenesence (40). Because DTH skin responses involve T cell proliferation, production of interleukin 2 and other lymphokines, and infiltration of the test site with mononuclear cells, aging of the immune system is reflected by the inability of elderly individuals to develop a proper DTH skin response. Given that most of the studies reviewed were performed in elderly subjects, most of whom had a compromised immune system, information about the effects of nutrients on DTH skin reactivity in younger healthy subjects is limited.

Mechanisms for the immune-enhancing properties of vitamins have not yet been completely elucidated, but it is clear that several measures of cell-mediated immunity may be modulated by nutrients (40, 61–63). In short, besides altering DTH skin responses, vitamins and β-carotene have been reported to induce increased numbers of natural killer cells and to enhance their activity, to increase interleukin 2 production, and to stimulate humoral immune responses by inducing higher antibody responses to influenza vaccine. However, these immunoenhancing effects of β-carotene were shown in elderly men but not in younger men (64, 65). Moreover, the effects of β-carotene on photoimmunosuppression reported by Fuller et al (56) and Herraiz et al (57) may be explained more by the photoprotective properties of β-carotene than by its immunostimulatory actions. Vitamin E and PUFAs have also been shown to decrease PGE_2 production, as a result of which T cell proliferation and function may be enhanced (50, 52, 66).

Most studies of the effects of nutrients on immune function used relatively high doses of micronutrients; therefore, improvements in immune responses may be due to pharmacologic effects rather than to the correction of nutritional deficiencies. Determination of the effects of long-term consumption of low-to-moderate amounts of vitamins and minerals in healthy individuals and of optimal nutrient intakes required to boost the immune system in individuals of different ages is needed.

IMPROVEMENT OF ATOPIC DERMATITIS AND PSORIASIS BY POLYUNSATURATED FATTY ACIDS

Besides their effects on cell-mediated function, PUFAs have been investigated for their antiinflammatory properties. The possibility of exerting a therapeutic effect in inflammatory skin diseases by manipulating the diet, particularly the content of PUFAs, is a subject of increasing interest. The background theory is that PUFAs play 2 important roles in the human body. They play a structural role, insofar as they are necessary for the fluidity, flexibility, and functionality of cell membranes and for the biosynthesis of intercellular lipids in the stratum corneum. In addition, they play a regulatory role—as precursors of eicosanoids (prostaglandins, thromboxanes, and leukotrienes). Atopic dermatitis is a multifaceted disease characterized by altered immune reactivity. Excessive inflammatory responses

have been suggested to involve a deficiency of antiinflammatory PGE_1 and defects in T cell differentiation (67). The amount of linoleic acid $(18:2n-6)$ was shown to be elevated at the expense of all of its metabolites (68). Psoriasis is also a common skin disorder, characterized by epidermal hyperproliferation accompanied by aspecific cutaneous inflammation. Several metabolites of arachidonic acid, such as PGE_2, 12-hydroxytetraenoic acid, and LTB_4, were reported to be increased and may be involved in the pathogenesis of these diseases through their inflammatory effects (69, 70).

Two families of essential fatty acids exist that can only be obtained through the diet: $n-3$ fatty acids (eg, α-linolenic acid and EPA) and $n-6$ fatty acids (eg, linoleic acid and arachidonic acid) (71). Whereas fish oils are rich in $n-3$ fatty acids, plant oils are the main sources of $n-6$ fatty acids. Supplementation of the diet with appropriate plant or fish oil has been hypothesized to prevent inflammation because of the ability of these oils to shift the eicosanoid balance to cyclooxygenase and lipoxygenase products with different, opposite, or weaker effects (69, 72, 73).

n−6 Polyunsaturated fatty acids

A typical Western diet contains high amounts of linoleic acid and γ-linolenic acid, whereas the amount of α-linolenic acid is relatively low. Certain plant oils, such as evening primrose seed oil (EPO) and borage seed oil, contain considerable amounts of linoleic acid and γ-linolenic acid and are unique because these oils also contain α-linolenic acid. The hypothesis on which the use of EPO is based suggests that subjects with atopic dermatitis cannot form adequate amounts of γ-linolenic acid (67, 68). During the past 2 decades, many studies have been published in which individuals with atopic dermatitis received a diet enriched with plant oils, particularly EPO, to evaluate the possible benefits of these PUFAs on this disease.

Wright and Burton (74) treated 60 adults and 39 children with atopic eczema with a placebo or EPO for 12 wk. Adults received 1440 mg linoleic acid/d and 180 mg γ-linolenic acid/d, or 2 or 4 times this dose. Children received either 720 mg linoleic acid/d and 90 mg γ-linolenic acid/d or twice this dose. A moderate improvement in clinical signs of atopic eczema was reported after supplementation, particularly after the highest EPO doses in both groups. Because the conversion of linoleic aid into γ-linolenic acid has been suggested to be blocked in patients with atopic eczema, the authors speculated that the presence of γ-linolenic acid in EPO may overcome this blockade.

A similar design was used by Bamford et al (75), who administered a higher dose of EPO than used in the study by Wright and Burton (74): 4320 mg linoleic acid and 540 mg γ-linolenic acid or twice this amount, or a placebo, to 123 subjects with atopic eczema for 3 mo. No significant effects were observed on the overall severity of the disease after supplementation. Bamford et al suggested that their findings, which were opposite those of Wright and Burton, were explained by differences in the severity of the skin lesions between the studies and in the clinical impressions used for diagnosis of atopic eczema.

Shalin-Karrila et al (76) treated 25 adult subjects with atopic eczema with a placebo or EPO, which provided 2880 mg linoleic acid and 360 mg γ-linolenic acid, for 12 wk. Supplementation with EPO improved affected skin sites. Even though the placebo also induced a reduction in inflammation, the effects were less than in the EPO-treated subjects. In addition, there was an increase in the amount of dihomo-γ-linolenic acid in plasma

phospholipids, whereas no increase was detected in the antiinflammatory mediator PGE_1, which is formed from dihomo-γ-linolenic acid. The assumption about a defect in the enzyme Δ^6-desaturase in subjects with atopic eczema, which is responsible for the conversion of linoleic acid into γ-linolenic acid, was not supported because the concentrations of γ-linolenic acid in plasma phospholipids were not different from those in healthy subjects. However, dihomo-γ-linolenic acid concentrations were higher in the EPO-supplemented group than in the healthy subjects. Although the authors suggested that EPO may be useful in the treatment of atopic eczema, conclusions were confusing because the placebo group took 3 times the amount of steroids as did the EPO-treated subjects and the initial status of eczema was worse in the EPO-treated group than in the placebo group. Therefore, the beneficial effects of EPO were difficult to ascertain.

In a study of 24 children aged 2–4 y with atopic eczema, children received a placebo or 3 g EPO/d, which provided 74.7% linoleic acid and 8.9% γ-linolenic acid (77). After 4 wk of EPO supplementation, symptoms of atopic eczema improved in 67% of the children, whereas no changes were noted in the placebo group. After EPO treatment, the ratio of linoleic acid to arachidonic acid decreased and plasma concentrations of dihomo-γ-linolenic acid and arachidonic acid increased significantly from baseline and were significantly higher than those in the placebo group. Because data on neutrophil and lymphocyte fatty acid composition were inconsistent, the authors concluded that the decreased ratio of linoleic to arachidonic acid in plasma may indicate a defect in Δ^6-desaturase. The ratio of linoleic to arachidonic acid is an approximate indicator of essential fatty acid desaturating activity, primarily of the enzyme Δ^6-desaturase. In atopic eczema there may be a desaturation defect resulting in altered ratios of plasma phospholipids. The same researchers conducted another study in which 12 children aged 2–4 y with atopic eczema received 3 g EPO/d for a longer time, 20 wk (78). An improvement in disease symptoms was seen beginning 4 wk after supplementation began. No clinical differences were observed between values observed at 4 and 20 wk of therapy. Increased plasma concentrations of γ-linolenic acid and arachidonic acid were detected as was a decreased ratio of linoleic to arachidonic acid at 4 wk, which was even more pronounced at 20 wk. Substantial changes in the fatty acid composition of neutrophils and lymphocytes were found and it was suggested that these changes resulted in alterations in the cell's immunologic activity, ultimately leading to inhibition of excessive cell-mediated immune responsiveness in atopic eczema.

In a large multicenter study (79) in which 179 patients with atopic dermatitis were treated with 4 g EPO/d, a clinical improvement was found in 62% of the patients and most patients showed a response within 12 wk. The results were based only on standardized clinical assessment forms completed by dermatologist. Nevertheless, it was concluded that EPO may work by slowly changing the composition of cell membranes toward normal.

Berth-Jones and Graham-Brown (80) used both EPO and fish oil to treat atopic dermatitis with the idea that both n−6 and n−3 fatty acids may modify eicosanoid metabolism in favor of less inflammatory prostaglandins and leukotrienes. A large study was conducted in which 102 subjects received 6 g EPO (3.9 g linoleic acid and 0.24 γ-linolenic acid), a combination of 5.2 g EPO and 1.3 g fish oil (0.20 g EPA and 0.13 g DHA), or a placebo for 16 wk. However, no improvements were shown in clinical severity scores, in the mean percentage of skin surface affected, and

in symptom scores. The authors believed that their study avoided all the methodologic and analytic problems of previous studies that reported beneficial effects of EPO (74, 77, 78).

n−3 Polyunsaturated fatty acids

Fish and marine oils are rich in long-chain n−3 PUFAs, particularly EPA and DHA. Because of the effects of n−3 PUFAs on immunologic and inflammatory diseases, an increased consumption of these fatty aids was hypothesized to lead to a suppression of immune and inflammatory responses. Many studies investigated the effects of n−3 PUFAs in relation to inflammatory diseases.

Ziboh et al (81) evaluated the health benefits of fish oil in psoriasis patients. They investigated whether supplementation of the diet of 13 psoriasis patients with fish oil containing n−3 PUFAs could suppress the generation of proinflammatory LTB_4. Daily intake of fish oil ranged from 60 to 75 mg, and each gram contained ≈180 mg EPA and 120 mg DHA. After 8 wk of supplementation, most of the patients showed a mild-to-moderate improvement in their lesions, which corresponded to a high EPA-DHA ratio in the epidermal, serum, and neutrophil lipids. No alterations in arachidonic acid in the epidermal lipids was evident. It was suggested that, particularly in neutrophils, a possible increase in the ratio of leukotriene B_5 (LTB_5), derived from EPA, to LTB_4, derived from arachidonic acid, was responsible for the reduction in inflammation.

The beneficial effects of fish oil were confirmed by Maurice et al (82). In their study, 10 patients with severe chronic psoriasis received 12 g EPA/d for 6 wk. A reduction in erythema and scaling was observed in 8 of 10 patients after treatment. Mean plasma and platelet ratios of EPA to arachidonic acid increased in subjects who responded to treatment. In addition, a marked suppression in LTB_4 production by polymorphonuclear leukocytes in vitro was shown, but only a modest improvement in clinical condition was seen. This implied the involvement of other mediators in the inflammatory process in psoriasis.

A much lower dose of fish oil, which provided 1.8 g EPA, was administered to 31 subjects with moderate-to-severe atopic dermatitis in a study by Bjørneboe et al (83). After 12 wk of supplementation, serum EPA concentrations increased. An overall reduction in itching and scaling was shown relative to the placebo group. Although arachidonic acid concentrations did not decrease, the ratio of n−3 to n−6 fatty acids in serum phospholipids increased after treatment. Competitive conversion of EPA instead of arachidonic acid may inhibit production of eicosanoids of the n−6 series and thus induce a favorable shift in eicosanoid formation. However, in a follow-up study of 27 psoriasis patients treated with 1.8 g EPA/d for 8 wk, there was no improvement in their clinical condition relative to the placebo group (84). Nevertheless, in the treated group, n−3 fatty acids in serum phospholipids increased and n−6 fatty acids decreased, whereas no changes in phospholipid fatty acids were detected in the placebo group. The authors concluded that the duration of treatment was possibly too short or the dose too low to detect any beneficial effect.

A similar low dose of fish-oil extract, which also provided 1.8 g EPA, was administered daily to 28 psoriasis patients for a longer time, 12 wk (85). At 8 and 12 wk, itching and erythema decreased significantly in the fish-oil group, whereas there was no significant change in the placebo group. The authors suggested that an increase in the dietary intake of fish oil and a reduction in the

intake of foods rich in arachidonic acid would be a useful treatment to counteract the exaggerated inflammation in psoriasis.

Supplementation of the diet of 80 patients with chronic psoriasis with 1122 mg EPA ethyl ester/d and 756 mg DHA ethyl ester/d resulted in an improvement in the overall skin condition and in individual disease indexes (pruritis, scaling, induration, and erythema) after 4 and 8 wk (86). Serum triacylglycerol concentrations decreased from baseline, but unfortunately no data on fatty acid composition were presented. It was suggested that the beneficial effects of polyunsaturated ethyl ester lipids from sea fish may have been mediated either by the formation of biologically less active leukotrienes and prostaglandins rather than those derived from arachidonic acid or by slowing down the inflammatory pathways by acting as a less favorable substrate for cyclooxygenase and lipoxygenase.

A large study of the effects of n−3 PUFAs was performed by Søyland et al (87). In this study, 124 psoriasis patients received either 6 g ethyl esters of very-long-chain n−3 fatty acids (51% EPA and 32% DHA as ethyl ester) or 6 g corn oil (26% oleic acid and 56% linoleic acid) for 4 mo. In the fish-oil group, scaling decreased and less cellular infiltration was seen. In the corn oil group, scaling and redness decreased and desquamation improved. Nevertheless, the clinical condition of the patients treated with fish oil did not improve more than in the corn oil group. In the fish-oil group, the ratio of n−3 to n−6 fatty acids increased in serum phospholipids, as did the ratio of EPA to arachidonic acid. In the corn oil group, only DHA concentrations increased and, remarkably, the increase in n−3 fatty acids corresponded to clinical improvement in this group only. The authors suggested that the inhibition of proliferation of T cells by arachidonic acid in corn oil and fish oil may explain the comparable clinical results in the 2 groups.

In a follow-up of this study (88), a similar treatment consisting of 6 g ethyl esters of very-long-chain n−3 fatty acids (51% EPA and 32% DHA as ethyl ester) or 6 g corn oil (26% oleic acid and 56% linoleic acid) was given to 120 subjects with atopic dermatitis. In both the fish-oil and corn oil groups, a significant improvement was seen in the mean clinical score and the subjective symptoms. Also, the ratio of n−3 to n−6 fatty acids in serum phospholipids increased significantly from baseline after fish-oil treatment, as did the ratio of EPA to arachidonic acid. Surprisingly, there was a significant increase in serum phospholipid total n−6 fatty acids in the corn oil–treated subjects, whereas n−3 fatty acids increased only slightly. In contrast, this resulted in a decrease in the ratio of EPA to arachidonic acid. Again, the authors suggested that the inhibition of T cell proliferation by n−3 and n−6 PUFAs may explain the beneficial effects of fish and corn oil in atopic dermatitis and are probably more important than is a change in the eicosanoid pattern.

Conclusion

Plant oils contain high amounts of linoleic and γ-linolenic acids, which are converted in the body to dihomo-γ-linolenic acid and subsequently to arachidonic acid. Daily supplementation with plant oils induces an increase in dihomo-γ-linolenic acid in neutrophil and epidermal phospholipids (89). This long-chain fatty acid can be metabolized into the lipoxygenase inhibitor 15-hydroxyeicosatrienoic acid and the antiinflammatory mediator PGE_1. Therefore, formation of these metabolites, which compete with the synthesis of the proinflammatory metabolites of arachidonic acid, LTB4 and PGE_2, may explain the beneficial effect of plant oils rich in n−6 fatty acids in inflammatory skin disorders.

Fish oil contains high amounts of EPA, which is converted into the lipoxygenase inhibitor 15-hydroxyeicosapentaenoic acid and LTB_5, thereby competitively inhibiting the formation of arachidonic acid metabolites (69, 72, 90). A shift in the balance of metabolites by competition with n−6 and n−3 fatty acids obviously influences the inflammatory response. Hence, the ratio of n−3 to n−6 fatty acids rather than the absolute amounts of the fatty acids was shown to be the determining factor in eicosanoid synthesis. Besides the effects of dietary fatty acids on lipid inflammatory mediators, suppression of cytokine production, ie, of tumor necrosis factor α and interleukin 1β, was shown previously (69, 91).

An important point in all studies of inflammatory skin disorders is that most patients use topical steroids. Thus, treatment with plant or fish oil must induce improvements greater than those induced by steroids. Steroids were shown to interfere with the ability to show an effect of PUFAs (70). Another important point was stated by Kunz et al (92), who treated patients with severe atopic dermatitis with EPA or placebo for 4 mo. Dermatologic assessment of the lesions showed an improvement in both the placebo and EPA groups. Kunz et al concluded that intensive and careful dermatologic control and guidance may be as important as the actual treatment in the management of patients with skin disorders.

Manipulation of cutaneous inflammation by dietary fatty acids is a complex task because the net effect of fatty acids on inflammation is an outcome of the interaction and balance between total fat, type of fatty acids, the ratios between different fatty acids, chain length, and the degree of saturation.

CONCLUDING REMARKS

Although it may be clear from this review that nutritional factors exert beneficial effects on the skin, it should be noted that antioxidant activity may shift to prooxidant activity, depending on the redox potential and the cellular and extracellular environments. Prooxidant effects were shown at high β-carotene concentrations or at high oxygen tension (93). The prooxidant potency under these circumstances may be due to the formation of β-carotene peroxyl radicals or to a faster rate of β-carotene autoxidation. Also, ingestion of supplemental doses of vitamin C may result in a prooxidant rather than an antioxidant effect, especially in conjunction with iron supplementation (94). However, in the presence of sufficiently high concentrations of coantioxidants, antioxidants normally delay or prevent oxidation of a substrate.

Excessive exposure to UV light is associated with many undesirable skin alterations. Increased sunlight exposure is also related to an increase in the incidence of nonmelanoma skin cancer (basal cell carcinoma and squamous cell carcinoma) (7). Although great importance has been placed on preventive measures, the role of nutritional factors in the primary prevention of nonmelanoma skin cancer is not promising, given the results of the few published studies (95, 96).

Besides the compounds mentioned in our review, many recent studies showed potentially interesting effects of some naturally occurring, less well investigated compounds that may improve skin conditions. Brosche and Platt (97) recently showed that consumption of borage oil improves cutaneous barrier function in elderly individuals, reflected by a decrease in transepidermal water loss. Garlic was shown to decrease lipid peroxidation and

to enhance concentrations of antioxidants and antioxidant enzymes in the circulation in animals and in vitro (98, 99). Green tea polyphenols were shown to reduce UV light–induced oxidative stress and immunosuppression (100). Significant antioxidant properties have been attributed to *Ginkgo biloba* (101) and to the plant extract *Polypodium leucotomos*, which can also inhibit UV light–induced lipid peroxidation (102). Moreover, this extract has been used orally to treat psoriasis and atopic dermatitis (103) and was recently reported to increase the MED and to protect against phototoxic reactions (104).

Many in vitro studies showed promising effects of nutritional factors on the skin. Nevertheless, extrapolation of in vitro data to the in vivo situation is often difficult. Moreover, in vivo studies of the effects of nutrients on human skin have mainly focused on indirect measures of skin function after supplementation, such as the assessment of the MED or DTH skin responses.

From this review it is clear that nutritional factors exert promising actions on the skin, protecting it against environmental influences and improving its function. Nevertheless, double-blind crossover intervention studies are necessary to investigate whether skin functions and conditions can be modulated by supplementing the diet with nutrients in amounts close to recommended dietary allowances. This may be important to substantiate claims and to offer an alternative to existing topical approaches for maintaining long-lasting healthy skin. ✥

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