Chapter 3
UV Irradiations, Micronutrient Supplementation, and Cutaneous Health: Overview

Saeed Hosseini and S. Ali Mostafavi

Key Points

- The most probable mechanism of photoprotective effects of vitamin C, vitamin E, β-carotene, lycopene, and omega-3 against UV light damages may be ascribed to their antioxidant functions, in fact they have the capacity to react with free radicals instead of vital skin structures hence protect skin from UV damages.
- Nevertheless, other mechanisms may be involved that are not fully clear so far.
- In addition to antioxidant capacity, at least some aspects of photoprotective effect of dietary nutrients may return to enhancement of cutaneous immune system mainly by enhancing the T-cell-mediated immune responses.
- The micronutrients which probably take part in this mechanism are notably the following: zinc, iron, copper, α-tocopherol, vitamin E, vitamin C, folate, carotenoids, and polyunsaturated fatty acids.

Keywords Skin aging • Sunburns • Fatty acid supplementation • Carotenoids

Introduction

Human skin condition and functioning may be influenced as a result of repeated exposures of edible and nonedible factors. One of these factors is the environmental UV irradiation. Frequent skin exposures to the environmental UV irradiations may cause acute sunburn symptoms and, through the mechanism of photooxidative damage, may lead to long-term damaging effects like photoaging. Photoaging is distinctive by wrinkles[1] and loss of skin flexibility.

[1] Slight lines or folds especially in skin of the face.

S. Hosseini, M.D., Ph.D. (✉)
Institute of Endocrinology and Metabolism, Shariati Hospital,
Fifth Floor, North Kargar Street, 1411413137 Tehran, Iran

Department of Nutrition and Biochemistry, School of Public Health, Tehran University of Medical Sciences,
Poursina Ave., Qods Street, 141556446 Tehran, Iran
e-mail: saeedhmdphd@hotmail.com

S.A. Mostafavi, M.s.
Department of Nutrition and Biochemistry, School of Public Health, Tehran University of Medical Sciences,
Poursina Ave., Qods Street, 141556446 Tehran, Iran

R.R. Watson and S. Zibadi (eds.), *Bioactive Dietary Factors and Plant Extracts in Dermatology*,
Nutrition and Health, DOI 10.1007/978-1-62703-167-7_3, © Springer Science+Business Media New York 2013

The other frequently exposed factors are different foods ingested at least three times daily. Besides the overall community health benefits, attempts to ensure the sound nutritional habits have additional advantages for skin appearance. In addition to skin color and scent, appearance of the skin can be determined by its surface consistency and physiologic characteristics such as elasticity, sweat, and sebum production.

Some branches of nutritional science deal with how nutrients can affect optimal skin condition,[2] and will be able to reach an accurate and deep intuitive understanding of the relationship between food ingredients and skin health [1, 2].

The ways by which nutritional factors influence skin condition lately have raised a lot of curiosity and interests. At least some part of our knowledge about nutrients and skin relationship come back to the past case reports of nutritional deficiencies and their cutaneous manifestations. Several vitamin and essential fatty acid deficiencies have apparent skin problems as a consequence. Recently, by public health promotions, the incidence of nutritional deficiencies has been decreased, but still imbalance and insufficient diets as a result of disease, aging, and the abuse of alcohol and drugs may affect health status and thus influence skin condition. In other words the most effective diet may not only stop skin disorders but may also promote skin condition.

In the previously published literature, food intake chiefly eating of fat, sugars, and spicy foods is frequently mentioned as influencing skin condition, though the methodical proof of this is limited.

When we go a little more deep into the content, we see that skin structures—lipids and amino acids—help to regulate skin pH. On the other hand, acidity of the skin makes it easier to keep from exogenous pathogens. Skin lipids, amino acids, and consequently its acidity is affected by endogenous and ecological factors, as well as aging, exposure to sunlight, chemicals, and mechanical damage [3].

Furthermore, dietary components, as frequently exposing agent, are declared to be one of the important factors which may influence our skin condition [4, 5]. For example, several cross-sectional studies have shown some associations between dietary components and skin aging. Maeve C Cosgrove and colleagues found that higher intakes of vitamin C and linoleic acid and lower intakes of fats and carbohydrates were associated with better skin-aging appearance [6].

In addition, hydration (existence of an abundant amount of water in the stratum corneum, i.e., outer layer of skin) is crucial for a soft and smooth skin manifestation. Sebum[3] and other epidermal lipids, collectively, supply the skin with a protective surface layer which can prevent skin dehydration [3].

The Role of Ultraviolet Irradiation and Reactive Oxygen Species in Relation to Elastin and Collagen in Skin Aging: Intrinsic Aging vs. Photoaging

Biologically, skin aging happens in two mechanisms: first, the senility, which progresses as years go by and originated from natural inner processes of loosing collagen, dehydration, and disintegration of flexible fiber network, which all together lead to dermis[4] chronic collapse and atrophy. The second is the aging procedure, which originates from environmental exposures. The most prevalent environmental agent is ultraviolet (UV) irradiation which causes photoaging.

In the genetic scale, UV exposure can induce elastin[5] promoter. This procedure facilitates the synthesis of elastin mRNA from the genomic material and leads to enhancement of elastin synthesis and

[2] Skin condition, normally, is defined as a mixture of some typical skin characteristics such as outer layer consistency, color, and physiologic features, such as hydration, sebum content, and surface acidity 1. Boelsma, E., et al., *Human skin condition and its associations with nutrient concentrations in serum and diet.* Am J Clin Nutr, 2003. **77**(2): p. 348–55.

[3] An oily secretion of the sebaceous glands.

[4] The thick layer of living tissue below the epidermis, containing blood capillaries, nerve endings, sweat gland, and other structures.

[5] An elastic, fibrous glycoprotein found in connective tissue.

accumulation of this fibric material in the upper and middle dermis, respectively. All these processes add to the clinical and morphologic changes pragmatic in photoaged skin [7].

Changes of intracellular and extracellular fluid can be seen in photoaged skin cells. Furthermore, dissociated elastin and fibrillin accumulate in the deep dermis, and a severe loss of interstitial collagens occurs in the matrix of the skin connective tissue. One of the pathogenic mechanisms which underlies these changes is the reactive oxygen species (ROS) generated by UV irradiations. The ROS exhaust and impair enzymatic and nonenzymatic antioxidant defense systems in whole body organs as well as in the skin. The ROS may cause everlasting hereditary changes in the genes. Furthermore, ROS can affect the skin cells' growth, development, and aging, and cause connective tissue dissociation by launching cytoplasmic signal transduction pathways in topical fibroblasts [2].

Tanaka and colleagues investigated the effects of ROS on the biosynthesis of connective tissue matrix ingredients, collagen and glucosaminoglycans (GAGs), in cultured human dermal fibroblasts. The ROS decreased collagen production and increased GAGs synthesis. Interestingly, these alterations were associated with the biological changes of connective tissue matrix components observed in photoaging skin. Furthermore, catalase and alpha-tocopherol completely prevented the ROS-induced alterations of collagen and GAGs biosynthesis, whereas superoxide dismutase had no effect on the ROS-induced changes. These findings show that ROS may be one of the factors that cause the biological changes of connective tissue matrix components observed in photoaging skin [8].

Sunburn Caused by Skin Exposure to UV Irradiation

Sunburn is the inflammation of the skin caused by overexposure to UV rays of the sun. Short-term exposure to the sun UV emissions can be abstained by the body defense system and is well tolerated by the skin. But above a specific threshold prolonged topical vasodilatation come into effect. Then the transportation of lymphocytes and macrophages into the tissue and beginning of inflammation process happen. This irritation becomes visible as reddening of the skin and it is clinically manifested as erythema.

One method of measuring the degree of UV radiation-induced erythema is determination of the minimal erythema dose (MED). One MED is the minimum quantity of energy needed to provoke a reliable, visible redness with fixed boundaries 16–24 h after contact with UV irradiation [5].

The Role of Micronutrient Supplementation in Sunburn and Skin Aging

Great amounts of micronutrients such as antioxidant vitamins and carotenoids exist in the skin and are proposed that help keep skin healthy [5]. There are strong evidences that skin damages from sunlight are well protected by dietary antioxidants [9]. Scientists have proven that supplementation with carotenoids, vitamin C and E before UV exposure may avoid the erythema related to sunburn. Reactive oxygen species may be generated in skin following UV exposure. Then, detrimental cascade reactions of photocarcinogenesis, photosensitivity, or early skin aging starts [10]. As a result, one mechanism of action underlying skin protective effects of antioxidants is scavenging reactive oxygen species [11]. But, this is not all a matter. More than a few dietary antioxidants exhibit biological properties other than antioxidant activity. Some fat-soluble nutrients can enter the nucleus and may alter cellular signaling pathways and may influence cell growth, development, and repair systems [12]. The basic aspects of skin aging and how carotenoids, vitamins, essential fatty acids, and trace elements affect this process is not well understood.

Some clinical trials have shown evidences of modulating skin health by oral supplementation with relatively high doses of vitamins, trace minerals, and fatty acids. Some other studies have investigated

the effects of fatty acids on skin condition, modulating (skin) immune function with oral micronutrient supplementation, and the protective effects of antioxidants against photoaging. Though, our knowledge about the effects of nutritional factors on skin condition is still rare.

Vitamins E and C and Selenium Supplementation

A few number of clinical trials carried out throughout the past two decades to inspect the photoprotective effects of dietary supplementation with vitamins C and E and selenium. In a double-blind, parallel, placebo-controlled trial carried out by La Ruche and Cesarini, 200 μg organic form of selenium (plus 16 mg copper) and a vitamin complex (with 14 mg α-tocopherol and 2,700 μg retinol) were examined for their ability to prevent sunburn cell formation in 16 healthy volunteers' skin exposed to ultraviolet radiation. After 3 weeks of supplementation with selenium, especially in association with vitamins, compared with the placebo group, all treatments with active ingredients, especially selenium in conjugation with antioxidant vitamins, provided limited protection against the formation of sunburn cells at a low irradiation dose (suberythemal). In high doses of UV irradiations (supraerythemal) these protective effects were not seen. And supplementation was ineffective in preventing light-induced erythema (skin reddening). It seems that photoprotective effects of these supplements can be attributed to improvement of antioxidant capacity of the skin cells [13].

Heinrich and colleagues showed that antioxidant supplements composed of vitamin E, selenium, and carotenoids promote measurable characteristics associated with overall skin structure as well as skin aging [14].

Karla Werninghaus, Mohsen Meydani, and colleagues investigated the photoprotective effects of 400 IU (295 mg) oral vitamin E (α-tocopherol acetate) or placebo against UV-induced epidermal damage. The results were evaluated at baseline, 1 month, and 6 months after supplementation. Not any significant difference was seen in the number of sunburn cells, produced by a threefold minimal erythema dose exposure, comparing with placebo. Throughout the study in spite of increasing serum α-tocopherol level, not any increases were detected in the skin, where photoprotection procedure must occur. This may logically explain why these investigators have not seen any protection in vitamin E group. Low vitamin E dose, Small sample size (12 subjects) and lack of other antioxidants to recycle α-tocopherol radicals may explain some logical reasons for this lack of success to show photoprotective futures of α-tocopherol [15].

In another trial, 40 healthy volunteers are divided in four trial groups. Two grams of α-tocopherol/day or 3 g ascorbate/day or a mixture of both vitamins (2 g α-tocopherol/day and 3 g ascorbate/day), or placebo was administered for 50 days. MEDs showed an obvious increase after supplementation with α-tocopherol and ascorbate mixture. MEDs also increased in subjects who received either vitamin alone or placebo but more slightly. Comparing with Werninghaus et al.'s study, in this investigation much higher doses of vitamin E were administered in combination with another antioxidant vitamin, and this caused the photoprotective effects to be more distinctive [16].

Vitamin E can modulate arachidonic acid metabolism and can affect eicosanoid system; in addition, it belongs to antioxidant family. All these characteristics may lead to the antiinflammatory properties of vitamin E and by this means harmonize the photoprotective effects of other antioxidants in the skin [5].

In another study by Eberlein-König et al., lower daily dosages of 671 mg vitamins E and 2 g vitamin C were administered for 8 days. In spite of this short study period and lower dose mean MEDs increased significantly compared with the placebo group. These investigators also showed a decrease in cutaneous blood flow in vitamin E plus vitamin C group, while there was an increment in cutaneous blood flow in placebo group.

Accordingly, it is inferable from these studies that short-term supplementation with fairly high doses of vitamin E and C (and maybe with combination of other antioxidant vitamins or minerals) may have photoprotective effects against UV radiations but not necessarily or significantly any effect on reddening of the skin [17].

Carotenoids Supplementation: β-Carotene and Lycopene

About 600 different carotenoids exist in nature, but we consume nearly 40 types of carotenoids in our diet especially by ingesting vegetable foods. Human gastrointestinal tract can absorb approximately 12 of these carotenoids, of which α-carotene, β-carotene, lutein, zeaxanthine, β-cryptoxanthin, and lycopene are among the most common. β-carotene is an important member of our nonenzymatic defense mechanisms against free radicals and potentially can degrade to yield vitamin A [18].

In addition to antioxidant function, carotenoids can modify absorption characteristics of the skin and immunomodulatory effects. β-carotene may have a direct photoprotective effect for the reason that it has the physical capacity to absorb radiance. Furthermore, some investigators reported nonvisible yellowish color of the skin following β-carotene ingestion that caused photoprotection by reflecting fractions of UV irradiations [5].

Photooxidative stress may induce reactive oxygen species, and one of the most efficient antioxidants which act by scavenging these particles are carotenoids. Both β-carotene and lycopene have been identified in the skin, but because of its regularity in our diet the β-carotene supplementation more frequently has been the subject of studies [19, 20].

Following the studies which showed the photoprotective effects of carotenoid supplementation, Stahl et al. studied to investigate whether intervention with a natural dietary source rich in lycopene keeps safe from harms of UV-induced erythema in humans.

Nine volunteers were fed daily with 40 g of tomato paste (containing about 16 mg/day of lycopene) for 10 weeks and were compared with the Control group ($n = 10$). A solar simulator induced Erythema at baseline, after 4 weeks and after 10 weeks. The measurable amount of erythema was evaluated by chromatometry. Serum carotenoid levels were measured by HPLC. Serum levels of lycopene increased in the trial group; the other carotenoids did not change significantly. At the end, in the tomato paste group 40% lower erythema formation was significant comparing with control group.

Therefore, these investigators succeeded to show clearly the protective effects of a commonly consumed dietary source of lycopene against UV light-induced erythema [21, 22]. In vitro investigations showed similar photoprotective effects in cell culture either. Furthermore, each carotenoid provides a level of protection against UV irradiations [23].

Thereafter, Aust et al. carried out another investigation to find whether different available lycopene sources are distinct from one another. In accordance they examined the photoprotective effects of synthetic lycopene in comparison with a tomato extract and a drink containing solubilized tomato extract in a way that all three groups ingested similar amounts of lycopene (about 10 mg/day) for 12 week. All the subjects were exposed by 1.25 minimal erythemal doses (MED) at dorsal skin (scapular region). The photoprotective effect was more noticeable in the two latter groups, which might be ascribed to phytofluene and phytoene, the carotenoids that are abundant in tomato extract and a drink containing solubilized tomato extract as well as lycopene [9].

In an approach to find the most efficient compound to fight against UV irradiations Greul et al. [24] examined the photoprotective effects of a mixture of several fat-soluble and water-soluble antioxidants including carotenoids (β-carotene and lycopene), vitamins C and E, selenium, and proanthocyanidins. To attain a mixture to be consumed safely for long term, the trial provided the antioxidants at near their physiological levels. Not any significant differences were seen between the intervention group and the placebo when minimal erythemal dose and chromametry of the skin were considered.

But matrix metalloproteinases 1 (MMP-1) and MMP-9 levels, two important enzymes that enroll in UV-induced sunburn processes, were significantly different between both groups after 2 weeks of intervention. In fact, supplementation with this antioxidant mixture caused a decrease in the UV-induced expression of MMP-1 and 9.

Wolf et al. investigated the effects of daily supplementation with 150 mg of oral carotenoids (60 mg β-carotene and 90 mg canthaxanthin) for a month. In spite of increments seen in the serum carotene concentrations, MEDs did not change significantly before and after the supplementation [25].

Cho et al. recently carried out a trial to examine the differential effects of low-dose and high-dose β-carotene supplementation on the human skin. Thirty and 90 mg/day of β-carotene were administered to 50 healthy subjects for 90 days. Type I procollagen, matrix metalloproteinase-1, and fibrillin-1 mRNA levels, and UV-induced thymine dimer and 8-hydroxy-2′-deoxyguanosine formation were assessed before and after the trial. Photoaging prevention signs and type I procollagen mRNA levels (4.4 ± 1.6 times increment comparing to the baseline) showed a significant difference just in the low-dose group. Significant decrease in the MED was observed only in the high-dose group. Significant reductions in UV-induced thymine dimer staining and 8-hydroxy-2′-deoxyguanosine staining were observed in the low-dose group in contrast to an increment in the high-dose group. Some investigators ascribe these new conflicting effects to the pro-oxidant effects of β-carotene spatially in high doses [26].

Is Supplementation with β-Carotene Safe?

Supplemental carotenoids are extensively used as skin protective agents against UV-induced erythema, yet little is known about safety and other effects of carotenoids on skin and whole body health [14]. In 1996, the results of an epidemiological cohort study carried out by Omenn et al. [27] raised a lot of worries about β-carotene supplementation safety. They observed the effects of β-carotene (30 mg) and vitamin A (25,000 IU of retinyl palmitate) mixture supplementation or placebo on respiratory organs of 18,314 smokers and asbestos workers. After about 4 years' monitoring, 388 new cases of lung cancer were detected (relative risk compared with placebo group: 1.25). Supplementation also increased the risk of death from lung cancer and cardiovascular disease. Finally the trial was stopped 21 months prior to what had intended to. But the criticizers emphasize that the methodology of this study was confounded by subject selection, since it was performed in high-risk participators (smokers and asbestos exposed workers). The next study (Physicians' Health Study) was performed on 22,071 middle-aged healthy male US physicians. On using 50 mg β-carotene supplementation on alternate days, not any significant differences in cardiovascular diseases, malignant tumor progression, and the overall mortality were seen [18].

So β-carotene supplementation is not a neoplasm or cardiovascular risk factor in healthy subjects, but long-term supplementation might be an additional risk factor for smokers. But the selection bias still remains in this study by attendance of the subjects who are more informed and concerned about their overall health, physicians, and the results cannot be referred to the normal society.

β-carotene is highly reactive and may slow down lipid peroxidation reactions in organic membranes. In fact β-carotene may make photocarcinogenesis worse under certain dietary and lifestyle circumstances. Photocarcinogenesis by β-carotene is diminished as the level of dietary fat decreases; this fact emphasizes on the possible association of lipid peroxidative reactions.

Does β-carotene really exhibit both pro-oxidant and antioxidant capacities? In fact, in photocarcinogenesis, intricate associations exist between the chemical mechanisms and the biological role of antioxidants. Still more studies with more precise design and more focus on mechanism of action are needed to solve this conflicting puzzle [28].

Omega-3 Polyunsaturated Fatty Acid Supplementation

Marine forms of omega-3 polyunsaturated fatty acids (PUFAs) are eicosapentaenoic acid (EPA; 20:5 omega-3) and docosahexaenoic acid (DHA; 22:6 omega-3). The most abundant marine sources are high-fat fishes such as mackerel, salmon, and sardine. However, optimistically, these sources are rare in most people's dietary plan. On the other hand, for reaching the most medical benefits it is important to attain a ratio of omega-6:omega-3 in our diet to about 3:1. This goal is so hard to achieve with mere dietary sources. So supplementation with omega-3 capsules is rational and sometimes indispensible under certain circumstances.

Omega-3 supplementations were the subjects of numerous clinical trials especially for intervening disorders with inflammatory mechanisms. But limited numbers of studies have evaluated the photoprotective effects of omega-3 supplementation against UV-induced erythema.

As discussed earlier, free radicals and lipid peroxidation are involved in the mechanism of erythema induced by Ultraviolet irradiation. Rhodes et al. studied the effects of supplementation with 10 g/day fish oil rich in omega-3 fatty acids (18% eicosapentaenoic acid and 12% docosahexaenoic acid) on UV-induced erythema and epidermal lipid peroxidation. Fifteen subjects participated for 6 months. MED increased significantly at the end but decreased again 10 weeks after the supplementation discontinued. Simultaneously with supplementation progression, skin capacity to lipid peroxidation decreased. In fact omega-3 fatty acids can be oxidized instead of vital inner structures and protect them from free radical damages [29].

To investigate the photoprotective effects of omega-3 fatty acids, Orengo et al. [30] supplemented ten volunteers' diets with 2.8 g EPA and 1.2 g DHA and compared the MEDs with ten subjects in placebo group after 4 weeks. MED increased significantly in the intervention group but prostaglandin E_2 (PGE_2) did not change significantly. These results confirmed the photoprotective effects of omega-3 fatty acids in short term.

One mechanism that could be involved in the photoprotective effects of omega-3 fatty acids is the mediators of vasodilatation, prostaglandins. Rhodes et al. [31] studied the effects of omega-3 fatty acids on UV-induced prostaglandin metabolism as well as potential photoprotective effect of omega-3 fatty acids in light-sensitive patients. Fish oil supplements enriched in omega-3 fatty acids were administered to 13 patients with polymorphic light eruption for 3 months. PGE_2 concentrations in skin fluid were assessed by collecting and analyzing the suction blister fluid. At the end MED increased significantly in the trial group. PGE_2 concentrations in skin fluid decreased after omega-3 supplementation both in irradiated and nonirradiated skin either. It can be inferred, that the inhibition of PGE_2 production in the skin is associated with the photoprotective effects of long-term omega-3 supplementation against UV irradiations.

Enhancement of Cutaneous Immune System by Micronutrient Supplementation

Sound nutritional status and optimal immune system performance are integrated. Sufficient vitamins and trace elements pools are needed for the immune system to work efficiently [32].

Micronutrient deficiencies prevent immune system from being expressed efficiently by the mechanism of attenuating the adaptive antibody and T-cell-mediated immune responses. This predisposes the host to infections especially in elderly, which in a vicious cause-and-effect cycle aggravates the micronutrient deficiency [33].

Lymphocyte count and delayed-type hypersensitivity (DTH) skin tests,[6] for instance, can be used for assessing the nutritional status of a patient. DTH skin responses include proliferation of T cells, interleukin 2, and other lymphokines production, and infiltration of the test position with mononuclear cells. The magnitude of DTH skin responses can be measured by diameter of the reddish area as a response to using a panel of typically facing antigens. But, these tests are complicated and are not routine in nutrition clinics [34].

Marginal nutrient deficiencies such as of zinc; iron; Vitamins B6, B12, folic acid, C, D, and E; and β-carotene are prevalent in older populations. Coexistence of such nutrient deficiencies in the elderly and immune function defects provide evidences that show they may be associated with each other[35, 36]. Scientists are on the verge of reaching an agreement that the supplementation with efficient doses of essential trace elements and vitamins may help to support the immune responses [36].

When we consider skin health as one of the components of immune system we should note that repeated and long-term sun exposures are ascribed to be related with humoral and cell-mediated immune responses and skin aging.

Several researches have been carried out mostly on the elderly to investigate whether supplementation with micronutrients can affect the skin immune function by using DTH test, but studies in healthy young people are scarce.

Researchers assumed that defects in the T cell-mediated immunity functions are responsible for at least some parts of immunosenescence in the elderly. As mentioned before DTH skin responses involve T-cell proliferation and on the other hand the elderly people are unable to respond appropriately to DTH test. So scientists concluded that aging of immune system may be associated with T-cell-mediated immunity defects.

Several cell-mediated immunity mechanisms are responsible for immune-enhancing characteristics of vitamins. Vitamins and β-carotene may enhance production of interleukin 2, increase the number and activity of natural killer cells and may affect DTH skin responses. Furthermore, it has been shown that supplementation with vitamins and β-carotene may provoke humoral immune responses. In fact oxidant-antioxidant balance is crucial for maintaining immune cell functions. It promotes the integration and functions of immune cells. To attain an optimal immune response in all age groups, sufficient amounts of antioxidant nutrients such as vitamin E, β-carotene, and glutathione are needed [37].

Vitamins C and E, selenium, copper, and zinc work against prospective damages of reactive oxygen species and adjust immune cell function. Furthermore, antioxidant vitamins and trace elements modulate cytokines and prostaglandins production. Abundant vitamins B6, folate, B12, C, and E; selenium; zinc; copper; and iron pool supports the proinflammatory Th1 cytokine-mediated immune response and a shift to an anti-inflammatory Th2 cell-mediated immune response is prevented. Through this mechanism, a desired immune response is provided by forenamed micronutrients supplementation. Vitamins A and D have significant roles in the cell-mediated as well as humoral antibody response. They are in favor of Th2-mediated anti-inflammatory cytokines. Vitamin A deficiency weakens both innate and adaptive immune responses. Vitamin D deficiency may increase vulnerability to infections as a result of defected localized innate immunity and impaired the antigen-specific cellular immune response. On the whole, poor status of previously mentioned micronutrients may lead to immunosuppression [33]. In addition to vitamins and minerals, macronutrients (notably, energy and protein) are effective on immune responses especially in the elderly [38].

By measuring DTH, some scientists reported that UV exposure is immunosuppressive. Investigators supplemented the healthy old men with zinc, β-carotene, α-tocopherol, folate, vitamin E, and vitamin C, and then measured DTH responses before and after UV exposures in different randomized double

[6] *Cell-mediated immune memory response.*

blind placebo-controlled trial. The more powerful DTH responses were associated with higher zinc and vitamin concentrations. In another words, higher plasma zinc and vitamin concentrations showed protective effects against UV exposures. These findings are in favor of the zinc and antioxidant vitamin supplementation role for immunomodulation [39–42].

Some investigators declare that dietary fatty acids can influence immune cell function by altering the fatty acid composition of membrane phospholipids in immune cells. Accordingly, the eicosanoids production and activity of membrane-associated enzymes may be influenced.

A reduction in the inflammatory mediator, $PGE_{2,}$ was reported following omega-3 PUFAs as well as vitamin E administration [43–45].

The long-term effects of supplementation in the healthy elderly and the effects of long-term consumption of the amounts of nutrients not above physiological and recommended levels on the immune system are not well understood and further investigations are needed.

Conclusion

Comparing with topical sunscreens which act only locally, supplementing regular diet with antioxidant vitamins, carotenoids, EPA, DHA, or a mixture, may protect the whole body against UV irradiation-induced damage. In spite of the contribution of natural dietary antioxidant nutrients, more amounts are needed above the amounts that exist in regular diets to attain the significant photoprotective effects. However, the level of skin sun-protection attains by antioxidant supplementation is much lower than the level of skin sun-protection can be achieved from the use of topical sunscreens. Up till now little is known about the photoprotective aspects of long-term consumption of physiological amounts of antioxidant vitamins or omega-3, the information which is important in developing functional foods [5, 32].

All the necessity of supplementation with omega-3 fatty acid comes back to omega-3 competition with omega-6 as a substrate for cyclooxygenase and lipoxygenase. If omega-3 fatty acids win the competition the result is production of less-active inflammatory mediators, prostaglandins, and leukotrienes. Lowest ratios of omega-6:omega-3 in the diet and hence in the skin lead to reductions in the synthesis of leukotriene B_4 (LTB_4) and PGE_2 or cytokines, such as interleukin 1 and tumor necrosis factor α. All these alterations lead to the obstruction of inflammatory cascades in the skin. Moreover, omega-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 (e.g., vitamin E and C and selenium) should also be consumed.

The most probable mechanism of photoprotective effects of vitamin C, vitamin E, β-carotene, lycopene, and omega-3 against UV light damages may be ascribed to their antioxidant functions; in fact they have the capacity to react with free radicals instead of vital skin structures, hence protect skin from UV damages. Nevertheless, other mechanisms may be involved that are not fully clear so far.

In addition to antioxidant capacity, at least some aspects of photoprotective effect of dietary nutrients may return to enhancement of cutaneous immune system mainly by enhancing the T-cell-mediated immune responses. The micronutrients which probably take part in this mechanism are notably the following: zinc, iron, copper, α-tocopherol, vitamin E, vitamin C, folate, carotenoids, and polyunsaturated fatty acids.

Still the body of our knowledge about the effects of nutrients on skin condition (especially in long-term intakes at recommended levels) and the actual need for supplementation is young and it is worthy of more attention and more long-term researches.

References

1. Boelsma E, et al. Human skin condition and its associations with nutrient concentrations in serum and diet. Am J Clin Nutr. 2003;77(2):348–55.
2. Scharffetter-Kochanek K, et al. Photoaging of the skin from phenotype to mechanisms. Exp Gerontol. 2000;35(3):307–16.
3. Dubertret L. Skin and environment. C R Acad Sci III. 2000;323(7):629–32.
4. Purba MB, et al. Skin wrinkling: can food make a difference? J Am Coll Nutr. 2001;20(1):71–80.
5. Boelsma E, Hendriks HF, Roza L. Nutritional skin care: health effects of micronutrients and fatty acids. Am J Clin Nutr. 2001;73(5):853–64.
6. Cosgrove MC, et al. Dietary nutrient intakes and skin-aging appearance among middle-aged American women. Am J Clin Nutr. 2007;86(4):1225–31.
7. Uitto J. The role of elastin and collagen in cutaneous aging: intrinsic aging versus photoexposure. J Drugs Dermatol. 2008;7(2 Suppl):s12–6.
8. Tanaka H, et al. The effect of reactive oxygen species on the biosynthesis of collagen and glycosaminoglycans in cultured human dermal fibroblasts. Arch Dermatol Res. 1993;285(6):352–5.
9. Aust O, et al. Supplementation with tomato-based products increases lycopene, phytofluene, and phytoene levels in human serum and protects against UV-light-induced erythema. Int J Vitam Nutr Res. 2005;75(1):54–60.
10. Krutmann J. Ultraviolet A radiation-induced biological effects in human skin: relevance for photoaging and photodermatosis. J Dermatol Sci. 2000;23 Suppl 1:S22–6.
11. Cesarini JP, et al. Immediate effects of UV radiation on the skin: modification by an antioxidant complex containing carotenoids. Photodermatol Photoimmunol Photomed. 2003;19(4):182–9.
12. Klotz LO, Holbrook NJ, Sies H. UVA and singlet oxygen as inducers of cutaneous signaling events. Curr Probl Dermatol. 2001;29:95–113.
13. la Ruche G, Cesarini JP. Protective effect of oral selenium plus copper associated with vitamin complex on sunburn cell formation in human skin. Photodermatol Photoimmunol Photomed. 1991;8(6):232–5.
14. Heinrich U, et al. Antioxidant supplements improve parameters related to skin structure in humans. Skin Pharmacol Physiol. 2006;19(4):224–31.
15. Werninghaus K, et al. Evaluation of the photoprotective effect of oral vitamin E supplementation. Arch Dermatol. 1994;130(10):1257–61.
16. Fuchs J, Kern H. Modulation of UV-light-induced skin inflammation by D-alpha-tocopherol and L-ascorbic acid: a clinical study using solar simulated radiation. Free Radic Biol Med. 1998;25(9):1006–12.
17. Eberlein-Konig B, Placzek M, Przybilla B. Protective effect against sunburn of combined systemic ascorbic acid (vitamin C) and d-alpha-tocopherol (vitamin E). J Am Acad Dermatol. 1998;38(1):45–8.
18. Bayerl C. Beta-carotene in dermatology: does it help? Acta Dermatovenerol Alp Panonica Adriat. 2008;17(4):160–2. 164–6.
19. Vahlquist A, et al. Vitamin A in human skin: II Concentrations of carotene, retinol and dehydroretinol in various components of normal skin. J Invest Dermatol. 1982;79(2):94–7.
20. Ribaya-Mercado JD, et al. Skin lycopene is destroyed preferentially over beta-carotene during ultraviolet irradiation in humans. J Nutr. 1995;125(7):1854–9.
21. Stahl W, et al. Dietary tomato paste protects against ultraviolet light-induced erythema in humans. J Nutr. 2001;131(5):1449–51.
22. Stahl W, et al. Lycopene-rich products and dietary photoprotection. Photochem Photobiol Sci. 2006;5(2):238–42.
23. Stahl W, Sies H. Carotenoids and protection against solar UV radiation. Skin Pharmacol Appl Skin Physiol. 2002;15(5):291–6.
24. Greul AK, et al. Photoprotection of UV-irradiated human skin: an antioxidative combination of vitamins E and C, carotenoids, selenium and proanthocyanidins. Skin Pharmacol Appl Skin Physiol. 2002;15(5):307–15.
25. Wolf C, Steiner A, Honigsmann H. Do oral carotenoids protect human skin against ultraviolet erythema, psoralen phototoxicity, and ultraviolet-induced DNA damage? J Invest Dermatol. 1988;90(1):55–7.
26. Cho S, et al. Differential effects of low-dose and high-dose beta-carotene supplementation on the signs of photoaging and type I procollagen gene expression in human skin in vivo. Dermatology. 2010;221(2):160–71.
27. Omenn GS, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med. 1996;334(18):1150–5.
28. Black HS. Pro-oxidant and anti-oxidant mechanism(s) of BHT and beta-carotene in photocarcinogenesis. Front Biosci. 2002;7:d1044–55.
29. Rhodes LE, et al. Dietary fish-oil supplementation in humans reduces UVB-erythemal sensitivity but increases epidermal lipid peroxidation. J Invest Dermatol. 1994;103(2):151–4.
30. Orengo IF, Black HS, Wolf Jr JE. Influence of fish oil supplementation on the minimal erythema dose in humans. Arch Dermatol Res. 1992;284(4):219–21.

31. Rhodes LE, et al. Dietary fish oil reduces basal and ultraviolet B-generated PGE2 levels in skin and increases the threshold to provocation of polymorphic light eruption. J Invest Dermatol. 1995;105(4):532–5.
32. Calder PC, Kew S. The immune system: a target for functional foods? Br J Nutr. 2002;88 Suppl 2:S165–77.
33. Wintergerst ES, Maggini S, Hornig DH. Contribution of selected vitamins and trace elements to immune function. Ann Nutr Metab. 2007;51(4):301–23.
34. Linn BS. Delayed hypersensitivity skin testing in nutritional assessment. Am Surg. 1987;53(11):628–31.
35. Chandra RK, Sarchielli P. Nutritional status and immune responses. Clin Lab Med. 1993;13(2):455–61.
36. Chandra RK. Impact of nutritional status and nutrient supplements on immune responses and incidence of infection in older individuals. Ageing Res Rev. 2004;3(1):91–104.
37. Meydani SN, et al. Antioxidants and immune response in aged persons: overview of present evidence. Am J Clin Nutr. 1995;62(6 Suppl):1462S–76.
38. Ahluwalia N. Aging, nutrition and immune function. J Nutr Health Aging. 2004;8(1):2–6.
39. Herraiz LA, et al. Effect of UV exposure and beta-carotene supplementation on delayed-type hypersensitivity response in healthy older men. J Am Coll Nutr. 1998;17(6):617–24.
40. Bunker VW, et al. Dietary supplementation and immunocompetence in housebound elderly subjects. Br J Biomed Sci. 1994;51(2):128–35.
41. Girodon F, et al. Impact of trace elements and vitamin supplementation on immunity and infections in institutionalized elderly patients: a randomized controlled trial. MIN. VIT. AOX. geriatric network. Arch Intern Med. 1999;159(7):748–54.
42. Meydani SN, et al. Vitamin E supplementation enhances cell-mediated immunity in healthy elderly subjects. Am J Clin Nutr. 1990;52(3):557–63.
43. Meydani SN, Hayek MG. Vitamin E and aging immune response. Clin Geriatr Med. 1995;11(4):567–76.
44. Meydani SN, et al. Vitamin E supplementation and in vivo immune response in healthy elderly subjects. A randomized controlled trial. JAMA. 1997;277(17):1380–6.
45. Wu D, et al. Effect of dietary supplementation with black currant seed oil on the immune response of healthy elderly subjects. Am J Clin Nutr. 1999;70(4):536–43.