Nutritional Clinical Studies in Dermatology

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ABSTRACT

Background & Aims: Nutrition has long been associated with skin health, beauty, integrity and aging through multiple pathways and cofactors implicated in skin biology. The onset and clinical course of various common skin diseases, especially acne, psoriasis, atopic dermatitis, and hair loss, have been suggested to be critically affected by nutrition patterns and habits. The relationship between acne and diet, predominantly the role of high glycemic load diets and dairy consumption have recently gained increased interest. Abnormal nutritional conditions such as obesity or malnutrition often manifest themselves by specific cutaneous features and altered skin function. Skin photoprotection, rendered by various nutrients, is well documented and appropriate nutritional supplementation has been shown to exert beneficial effects upon impaired skin integrity, restore its appearance and promote skin health. It is our intention to provide a comprehensive review of the most recent information on the role of nutrition for common skin diseases and regulation of skin biology.

Methods: Nutritional clinical studies in dermatology have been reviewed using the MedLine literature source and the terms "diet" or "nutrition" and "skin".

Results & Conclusions: The data on the relationship between nutrition and skin are until now controversial and much more work is needed to be done to clarify possible etiological correlations.

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INTRODUCTION

The structural integrity, functional capacity, and regenerative potential of the human skin are known to be influenced, to a variable extent, by a plethora of factors, which thus greatly affect our appreciation of its overall appearance and our perception of its health and beauty. Heredity, sunlight, environmental or occupational exposure, chronic disease, medications, drug abuse, dietary habits, hormonal supplementation, psychosomatic stress, and poor socioeconomic conditions have all been implicated in the pathophysiology of skin abnormalities and aging. Nutrition has historically been one of the earliest and most important factors associated with skin health. However, the degree of its impact upon skin physiology, as well as the mechanisms involved in various nutrition-dependent alterations in skin structure and function, remain highly controversial.

Practical hardships in explicitly establishing a causative association between consumption of specific nutrients or food products and their potential effects on the skin have been hampered within clinical research, even when this relationship might appear straightforward or highly reasonable.

In this article, we thoroughly analyze available evidence derived from the most important clinical nutritional studies with regard to the human skin and we provide scientifically sound and clinically relevant conclusions based on emerging knowledge in this very challenging area of research.

Effects of Nutrition on Specific Skin Diseases

Nutrition and acne

Historically, the association between acne and nutrition has been highly controversial. The studies of Fulton et al,[1] in 1969 and Anderson[2] in 1971 failed, at the beginning of the second half of the century, to show any associations between diet and acne. The former,[1] was a cross-over subject-blind interventional study of 65 adolescents who received either a chocolate bar or a control bar with similar amounts of sugar and fat in both bars; all subjects exhibited a similar glycemic index and glycemic load. The latter,[2] a case series study of 27 students did not show any effects of various foods (chocolate, milk, toasted peanuts or cola) during a short study period of only 1 week.

The first serious randomized placebo-controlled dietary study was provided by Smith et al,[3] who demonstrated a link between high glycemic load carbohydrate intake and acne. Smith et al,[3] demonstrated significant improvement of acne severity in 23 Australian males aged between 15-25 years, adhering to a low glycemic load diet. The low glycemic load diet resulted in significant reduction in

weight, body mass index, free androgen index, and increased IGF binding protein-1 (IGFBP-1) serum levels coupled with reduced bioavailability of free IGF-1 and improved insulin sensitivity.[4]

Bowe et al,[5] have also recently provided compelling arguments on the association between acne and high glycemic load diets, as well as weak evidence for an association between dairy ingestion and acne. In a meta-analysis of the relationship between diet and acne, Spencer et al,[6] reported that, out of 27 relevant studies, 21 were observational and only six were properly controlled clinical trials. Substantial evidence in support of an association between acne and selected foods has been found for high glycemic carbohydrates. High glycemic carbohydrates, milk and other insulinotropic dairy products appear to share a common endocrine mechanism of action implicated in acne pathogenesis. Both high glycemic load diets and insulinotropic dairy products have been shown to raise serum insulin and free insulin-like growth factor-1 (IGF-1) levels and to induce insulin resistance (Figure 1).[3, 7-9]

There is ongoing controversy on the role of milk and dairy consumption as an aggravating factor in acne pathogenesis.[10-12] In 1949, a case series published by Robinson[13] on 1925 subjects with acne, reported that milk was the most commonly implicated food in acne flares. Although the number of studied subjects was high, no reliable data or statistical analyses had been provided. Indirect evidence has been presented by Cordain et al,[14] who did not observe acne in any of 1200 Kitavan of Papua New Guinea and 115 Aché of Paraguay subjects who do not consume high glycemic load diets and dairy products.

Adebomowo et al,[15-17] presented a retrospective cohort study of 47,355 women using a food frequency questionnaire of distant dietary intake and subject report on physician-diagnosed severe acne. They found that acne was positively associated with intake of milk, particularly skim milk, instant breakfast drink, sherbet, and cottage cheese, all known as dairy products associated with elevated plasma insulin concentrations. The weakness of this study mainly consists of its retrospective design, memory-based recall of diet and acne. Therefore, any association between dairy products and acne remains debated and requires further investigation.

Nutrition and atopic dermatitis (AD)

Development, clinical sequelae and remission / relapse cycles of AD have been attributed to food macro- and micronutrients.[18] Specific nutritional interventions using probiotics (*Lactobacillus* species, such as *Lactobacillus rhamnosus* GG, *Bifidobacterium lactis* Bb-12, *B. breve* M-16V or *L. fermentum* VR1-003PCC) are described in some studies as exerting beneficial effects on the treatment and/or prevention of AD, with a decrease in SCORAD (Scoring Atopic Dermatitis) or a decrease of the frequency of AD in the first two years of life.[19]

Trials evaluating early life oral probiotic administration for eczema prevention are more consistently positive and promising than the eczema treatment studies. Thirteen randomised controlled trials evaluating various probiotic bacteria used alone or in combination with other probiotics have now been reported.[20-32] Overall, the collective data from these studies suggest that probiotic treatment during late pregnancy and early postnatal life reduces the risk of eczema.

"Very recently, epidemiological evidence suggests that multivitamin use is associated with longer telomere length, a marker of biological aging, in women."

The use of oral probiotics for promoting immune responses in the skin has been explored in relation to ultraviolet light induced skin damage, where one clinical study suggested that probiotic treatment may have a role in promoting recovery from such damage in those most susceptible to it.[33]

The alleviation of AD has also been targeted by several oral intervention studies with Essential Fatty Acids (EFAs). Van Gool et al,[34] summarized that early supplementation with GLA (γ-linolenic acid) in children at high familial risk, tends to alleviate the severity of atopic dermatitis in later infancy in these children. Van Gool et al, also performed a meta-analysis of placebo-controlled EFA trials and concluded that the effects of EFAs were negligible.[35] In addition, Foster et al,[36] performed a similar analysis on the particular effect of borage oil on AD. He reached the conclusion that a major clinical effect is unlikely. However, he noted that it may be useful in some patients with less severe AD and could be used as maintenance treatment for prevention of flare up in milder cases.

Linnamaa et al,[37] concluded that dietary supplementation with blackcurrant seed oil transiently reduced AD prevalence. Kitz et al,[38] has examined γ-linolenic acid (GLA)-supplementation, which seemed to reduce total IgE in the first year of life; however, it could not prevent AD. In the study of Callaway et al,[39] a single-blinded crossover study on AD subjects using hempseed oil compared with olive oil, reduced skin dryness and skin itching was observed in the hempseed oil group; however, it is noteworthy to mention that hempseed oil also contains high amounts of other PUFAs as α-linolenic acid. Two additional studies have demonstrated improvement of barrier function after supplementation by GLA in elderly subjects[40] and in younger population,[41] as well.

In a recent report, Koch et al,[42] have shown the beneficial effect (decrease of SCORAD) of docohexaenoic acid supplementation in atopic eczema. In a similar fashion, oral evening primerose oil

was reportedly of benefit to patients with moderate to severe eczema,[43] whereas dietary supplement with fish oil has been shown to improve clinical management of psoriasis and eczema.[44]

Nutrition and other skin diseases

Diet has been postulated to participate in the etiology and pathogenesis of psoriasis, a T-cell-mediated inflammatory disease, characterized by hyperproliferation and poor differentiation of epidermal keratinocytes. Protracted fasting, low-energy and vegetarian diets were shown to improve psoriasis symptoms in some studies, as were diets rich in omega-3 polyunsaturated fatty acids from fish oil, possibly by acting in qan "anti-inflammatory" fashion and thus by modifying the polyunsaturated fatty acid metabolism and eicosanoid profile[44].

On the other hand, it has also been established that severe psoriasis may lead to nutrient depletion, especially of protein, folate, and iron. Nutrient deficits have been attributed mainly to accelerated losses from hyperproliferation and desquamation of the epidermal layer of patients with psoriasis. Psoriasis-induced nutrient deficits and impaired nutrition aggravate disease manifestations or predispose to skin comorbidities.[45,46] The role of selenium has long been underscored in regards to duration and severity of psoriasis, however such an association appears to exist in patients with long standing psoriasis of more than 3 years.[47-50] In several studies, dietary fish oil has been found to have beneficial effect on psoriasis, but dietary supplementation with very-long-chain n-3 fatty acids was no better than corn-oil supplementation in treating psoriasis.[51]

Hair loss is a very common problem for both genders, affecting up to 80% of men and 50% of women in their life time.[52, 53] Nutrients rich in antioxidants, primarily polyunsaturated fatty acids, zinc, taurine and plant polyphenols, have been shown to preserve a more balanced hair cycle, leading to decreased hair loss and increased hair density along with an improvement of hair quality.[54]

In recent decades, the incidence of subjects presenting reactive skin has considerably increased in industrial countries. Reactive skin is characterized by marked sensitivity of the skin to physical (heat, cold, wind) or chemical (topical product application) stimuli and occasionally by impaired ability for skin barrier function recovery. A recent study demonstrated that after 43 days of supplementation, a specific probiotic called *L. aracasei*, significantly decreased skin sensitivity compared to placebo, and has also increased the recovery rate of the skin barrier function induced by mechanical disruption.[54]

Nutrition and photoprotection

The most frequent damage induced by UV exposure is sunburn, and there has been evidence of its prevention by nutritional supplementation. Beta (β)-carotene (from 15 to 180 mg/day) and lycopene (up to 10 mg/day), two efficient oxygen quenchers, have been shown to prevent sunburn in humans.[55-58] Systemic administration of antioxidants such as vitamin C (2 mg/day) and E (1000 IU/day), as well as dietary fish oil (2 g/day), rich in ω-3 free fatty acids, increased minimal erythema dose.[59, 60] The effect of fish oil on UV-induced inflammation may be partially explained by its ability to reduce prostaglandin E2 levels.[61] Polyphenols provided by ingestion of cocoa rich in high flavanol (326 mg/day) reduced UV-induced erythema.[62] *Polypodium leucotomos* (7.5 mg/kg of body weight), a tropical fern plant used traditionally in Central America for the treatment of inflammatory disorders, has also been shown to counteract the erythematogenic effect of UV exposure.[63]

UV exposure can lead to both direct and indirect DNA damage. The major direct DNA damage is the release of cyclobutane pyrimidine dimers (thymine dimers and 6-4 photoproducts). Placzek et al,[64] have shown that oral administration of vitamin C (2 mg/day) and E (1000 IU/day) during a period of 3 months, had a protective effect against UV-induced thymine dimers. Photoprotection obtained by nutrients is well documented. Skin exposure to ultraviolet (UV) leads directly or indirectly - through the generation of reactive oxygen species - to a large range of photodamage affecting cellular lipids, proteins and DNA. It is involved in erythema appearance, premature skin aging, photoimmunosuppression and skin cancer.[65-67]

UV exposure also causes local and systemic immunosuppression, and several mechanisms are involved in this deleterious effect, among which UV-induced depletion of Langerhans cells (LC), the major antigen presenting cells in the skin.[68] A placebo controlled study demonstrated that β-carotene (30 mg/day) protects against photoimmunosuppression.[69] Oral administration of *Polypodium leucotomos* (1080 mg) prior to UV exposure seemed to protect CD1a+ cell density and preserved dendritic morphology of immune cells.[70] More recently, oral supplementation with the probiotic strain *Lactobacillus johnsonii* has been shown to accelerate recovery of human skin immune homeostasis after UV induced. This specific strain associated with carotenoids (β-carotene: 4.8 mg/day; lycopene: 2 mg) was also able to counteract UV-induced decrease of LC density in human volunteers.[71]

There is ample emerging evidence that probiotic strains can modulate the immune system of the skin in a beneficial way, leading to the preservation of the skin homeostasis. This could enable the design of novel nutrition-based compounds and interventions, for the prevention of UV-induced damaging effects.[72]

Malnutrition and Obesity

Primary nutritional deficiencies might be considered rare, but they are still prevalent in developing countries and should also be considered in developed countries, in populations genetically predisposed to various disease states.[73] The vast majority of malnutritional syndromes in current medical practice relate to secondary elementary or macro-nutrient deficits due to pre-

TABLE 1.

Cutaneous manifestations of nutritional disorders	
Malnutrition	**Obesity**
acrocyanosis	acanthosis nigricans
acrodermatitis entheropathica	acrochordons
alopecia	adiposis dolorosa
carotenoderma	eruption of psoriasis
hair fragility	cellulitis
hypertrichosis	chronic venous insufficiency
lanugo-like body hair	fat redistribution
livedo reticularis	hidradenitis suppurativa
nail fragility	hirsutism
paronychia	keratosis pilaris
pellagra	lymphedema
perniosis	plantar hyperkeratosis
petechiae	process of wound healing
Raynaud's phenomenon	skin infections
Russell's sign (knuckle calluses)	striae distensae
xerosis	tophaceous gout

maturity (infants), or in patients with long-term total parenteral nutrition, gastro-intestinal pathologies like Crohn's disease, neoplasias, cystic fibrosis, intestinal bypass procedures, chronic alcoholics, as well as those in restrictive diets.[74] The skin is very commonly involved and is often one of the first organs affected in nutritional deficiency, thus providing a key to the diagnosis. The most commonly encountered nutritional deficit disorders relate to zinc, biotin, essential fatty acids, protein deficiency and kwashiorkor (common in patients with the HIV infection).[75]

Many authors have reported skin signs in anorexia nervosa (AN) and bulimia nervosa (BN).[76-79] Cutaneous manifestations constitute somatic expression of underlying disorders, vomiting, abuse of drugs such as laxatives and diuretics, and of psychiatric morbidity. Gupta et al,[80] have classified skin manifestations of eating disorders into four groups: those caused by starvation and/or malnutrition, those due to self-induced vomiting, findings caused by drug consumption and those caused by concomitant psychiatric illness. Based upon his data, Glorio[81] has further identified two main groups of signs: a) frequent signs (xerosis, alopecia, caries, opaque and fragile hair, nail fragility) and b) guiding signs (hypertrichosis, Russell's sign, perimylolysis, self-induced dermatitis). Hediger et al,[82] documented that a body mass index (BMI) of less or equal to 16 should be considered a threshold value at or beyond which skin changes are more frequent.

There are numerous symptoms of starvation, which are expressed as cutaneous manifestations (Table 1). [83] Lanugo-like body hair is a frequent sign in AN, especially in younger patients. It presents as fine, downy, pigmented hairs on the back, abdomen and forearms. It is not a sign of virilization and has been associated with decreased activity of the 5α-reductase enzyme system, probably due to hypothyroidism and reduced serum levels of IGF-1. Acne might be referred to starvation, but could itself be a risk factor for AN. In fact, in psychologically vulnerable girls, a new diet behaviour, adopted to control their acne, might actually lead to weight loss and AN. Carotinosis is due to marked ingestion of carotenoid-rich vegetables low in calories. Acrocyanosis could represent a more extreme form of heat conserving mechanism not uncommon in anorectics. Raynaud's phenomenon and perniosis have been also reported due to endocrine complications. Nail fragility, longitudinal ungueal striae, onychocryptosis, periungueal erythema, prurigo pigmentosa and pompholyx have also been reported. The most characteristic cutaneous sign in purging type AN, is the Russell's sign (knuckle calluses). The lesions involve calluses on the dorsal aspects of the dominant hand induced by the patients' repeated introduction of the hand into the mouth.[84,85]

Obesity has been associated with multiple skin disorders, including altered skin barrier function, sebaceous gland physiology and sebum production, sweat gland biology and regulation, lymphatic drainage, collagen structure and functional properties, process of wound healing, distribution and pathobiology of subcutaneous adipose tissue, as well as impaired microcirculatory supply.[86] There are numerous characteristic dermatologic signs in obesity, particularly pronounced in morbid obesity and when co-morbidities like the polycystic ovaries syndrome are present, including acanthosis nigricans, acrochordons, striae distensae, adiposis dolorosa, fat redistribution, lymphedema, cellulitis, skin infections, hidradenitis suppurativa and others (Table 1).[87,88]

Nutrition, skin aging and skin beauty

Increased life expectancy is associated with a need to appear healthy and handsome. Many attempts have been made to improve skin health and beauty by changing or by supplementing the diet. In 2001, Boelsma et al,[89] reviewed the effects of vitamin, carotenoid and fatty acid supplementation in optimizing skin condition and preventing skin diseases and concluded that nutritional factors show potential beneficial actions on the skin. Very recently, epidemiological evidence suggests that multivitamin use is associated with longer telomere length, a marker of biological aging, in women.[90] In 2001, Purba et al,[91] described that actinic damage, especially skin wrinkling, may be associated with food habits. In that study, high intake of vegetables, legumes and olive oil appeared to be protective against cutaneous actinic damage. In another report, higher intake of vitamin C and linoleic acid, as well as lower intake of fat and carbohydrate, were shown to associate with better skin appearance.[92]

TABLE 2.

"Take home" messages
1. There is compelling evidence for a positive association between acne and high glycemic load diets, as well as weak evidence for such an association between dairy ingestion and acne.
2. Both high glycemic load diets and dairy products are linked to raised serum insulin levels and free insulin-like growth factor-1, thus contributing to the pathogenesis of acne.
3. Specific nutritional interventions using probiotics (Lactobacillus species) are described as exerting beneficial effects on the treatment and/or prevention of atopic disease.
4. Early supplementation with γ-linolenic acid in children at high familial risk tends to alleviate the severity of atopic dermatitis in later infancy in these children.
5. Protracted fasting, low-energy and vegetarian diets were shown to improve psoriasis symptoms in some studies, as were diets rich in omega-3 polyunsaturated fatty acids from fish oil.
6. Nutrients rich in antioxidants, primarily polyunsaturated fatty acids, zinc, taurine and plant polyphenols have been shown to decrease hair loss and enhance hair quality.
7. β-carotene and lycopene, two efficient oxygen quenchers, have been shown to prevent sunburn in humans.
8. Xerosis, alopecia, hair and nail fragility are frequent cutaneous manifestations of anorexia nervosa.
9. Acanthosis nigricans, striae distensae, adiposis dolorosa, cellulitis and skin infections are common cutaneous manifestations of obesity.
10. Higher intake of vitamin C, linoleic acid, lycopene and soy isoflavones, as well as lower intake of fat and carbohydrate, were shown to associate with improved skin appearance

Yamakoshi et al,[93] investigated the effect of oral intake of a proanthocyanidine enriched extract (201 mg/day over 6 months) on facial hyperpigmentation in women and demonstrated that this extract was able to improved chloasma determined by clinical evaluation as well as by using colorimetric method. Oral fish polysaccharides (3 x 250 mg/day over 8 weeks) associated with an antioxidant mix have been shown to improve dermal thickness, skin wrinkling, color and viscoelasticity after 2 months of supplementation.[94]

Silicon (choline-stabilized orthosilicic acid; 20 mg/day) taken orally during 20 weeks enhanced skin microrelief and mechanical properties in women with photo-damaged skin.[95] A combination of lycopene (6 mg), vitamin C (60 mg) and soy isoflavones (50 mg) has been shown to maintain skin density, improve skin firmness, microrelief, hydration and tone in menopausal women.[96-98]

Several antioxidants have demonstrated a skin photoprotection effect including flavanols, carotenoids, tocopherols, and vitamin C.[99,100] Flavonoids are widespread in nature and available from dietary sources such as cocoa, green tea, soy, berries and a variety of fruits.[101] Flavonoid-containing phytomedicals bare anti-inflammatory and anti-allergic activities but also exhibit a variety of other biological activities.[102]

Cocoa products that contain high flavonoid levels upon ingestion contributed to endogenous photoprotection and improvement of dermal blood circulation.[103] In addition, cocoa flavanols seemed to be primarily responsible for ameliorating skin surface cosmetic parameters (skin density and thickness, decrease of skin roughness) and hydration. In in vitro and animal studies, tea flavanols, orally or topically, ameliorated adverse skin reactions following UV exposure, including skin damage, erythema and lipid peroxidation.[104] Positive results were also observed in topical applications of green tea polyphenols onto human skin.[105,106] Perhaps this can constitute some evidence to support human clinical studies on the consumption of dietary flavonoids from tea for improvement of photoprotection and skin quality.

Another study[107] examined the effect of the ingested flaxseed or borage oil. Skin irritation, blood flow, skin hydration were ameliorated with flaxseed or borage oil ($P< 0.05$). Transepidermal water loss was decreased in both groups and surface evaluation of living skin revealed that roughness and scaling of the skin were significantly decreased with flaxseed and borage oil, when comparing week 0 and week 12.

CONCLUSION

For a considerably long time, nutrition was regarded as one of the principal factors influencing overall "well being" and the perception of "health" in humans. The skin is the largest and heaviest endocrine organ in the body.[108] The skin provides a first impression about one's state of biological condition, age and certainly beauty, as well as reflects psychosomatic balance and stress status, thus it constitutes a prime target for ingested nutrients, either directly or indirectly. Increasing clinical appreciation of the growing significance of nutritional composition, patterns, habitual exposure and its interplay with multiple hormonal mediators, pathway co-factors, structural elements and functional parameters of the skin, have been underscored by emerging evidence from the literature. Not only nutritional deficiencies or excesses have been shown to predispose to onset or recurrence of various dermatologic disorders, but they are also involved in their pathogenesis and clinical manifestations. On the other hand, accurate knowledge and appropriate handling of our potential to manipulate individual nutritional aspects as treatment modalities in skin pathologies could provide a powerful and patient-friendly tool to prevent, alleviate or even cure common skin diseases.

DISCLOSURE

Apostolos Pappas, PhD works for the Johnson & Johnson Skin Research Center, CPPW, a division of Johnson & Johnson Con-

sumer Companies, Inc., Skillman, NJ.

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