Use of Vitamins and their Derivates in the Treatment of Cutaneous Disorders

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Abstract: Vitamins represent fundamental substrates for various physiologic functions occurring in human body. This review seeks to highlight their relevance in skin biology and to describe the cutaneous manifestations correlated with their deficiency.

Keywords: Vitamin deficiency, psoriasis, vitamin A, vitamin B, vitamin C, skin physiology.

INTRODUCTION

The intake and the metabolism of nutrients in appropriate proportion provide the substrates necessary for physiologic functions. Derangements of this normal proportion and balance lead to disease states that can produce cutaneous manifestations with an involvement of multiple organs [1]. Because of the importance of nutrients for cellular metabolism in a variety of tissues, this review provides an overview on vitamins and their role in cutaneous disorders.

VITAMIN A

Vitamin A, retinol, is a fat-soluble vitamin that is required for retinal photoreceptor function, hematopoiesis, embryonic development, skin cell differentiation, immune system function and gene transcription. Vitamin A cannot be synthesized; it must be obtained through animal products, such as cow's milk, liver, eggs, fish oils, as retinyl esters. Retinyl esters are converted to retinol and absorbed in the ileum. After absorption, a small percentage of retinol is converted to its biologically active form, all-trans retinoic acid (tretinoin), through an intermediary, retinaldehyde. Most of retinol is converted to retinyl ester, its storage form [1, 2]. Two vitamin A derivates, namely retinal and retinoid acid, are used for therapeutic purposes.

Retinoid signaling is mediated by various nuclear receptors, which belong to superfamily of nuclear receptors that act as transcription factors, which promote the physiologic effects on DNA transcription. These receptors fall into two classes, the retinoic acid receptor (RARs) and the retinoid x receptor (RXRs). Human skin expresses predominantly RAR-γ and RXR-α [3-5].

Vitamin A deficiency is the most common cause of preventable childhood blindness. Xerophthalmia is initially characterized by defective dark adaptation and night blindness. Perpetuating vitamin A deficiency determinates xerosis, ulceration and perforation of the cornea, prolapse of the iris, and, ultimately, blindness [6,7]. The typical cutaneous hypovitaminosis A manifestation is phrynoderma, characterized by xerosis and keratotic follicular papules preferably located on the flexure and traction side of the upper arms, and on the trunk and nape (Table **1**). Differential diagnoses include pityriasis rubra pilaris and lichen spinulosus. Phrynoderma is probably based on additional deficiencies of unsaturated fatty acids, vitamin C, and B-complex vitamins [8-13].

Vitamin A and its analogs in cosmetic applications are among the most important agents used for skin care. They have been used topically in treating acne and photodamage skin and they have been tested for the topical treatment of striae, cellulitis, and wound healing [14-20]. In addition, they represent an approved and well-established treatment for psoriasis, used both orally and topically as monotherapy or in therapeutic combinations.

Use of Retinoids in the Treatment of Acne

Acne is a common skin disease showing a multifactorial pathogenesis, which includes increased

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Table 1: Disorders and Clinical Manifestions Related to Vitamin Deficiency

Vitamins	Disorders associated with vitamin deficiency
VITAMIN A	Xerophthalmia, Phrynoderma
BETA-CAROTENE	Immunosuppression
VITAMIN B1	"Beriberi" disease, Impaired wound heeling, Wernicke encephalopathy (acute) and Korsakoff syndrome (chronic)
VITAMIN B2	Ariboflavinosis (angular cheilitis, pharyngitis, glossitis, seborrheic dermatitis, photosensitivity), Oro-oculo-genital syndrome
VITAMIN B3	Pellagra (dermatitis, dementia, diarrhea, death)
VITAMIN B6	Seborrheic eruption , Oral symptoms (glossitis, stomatitis, cheilitis, aphtha), Conjunctivitis, Intertrigo, Pellagra-like dermatitis (erythema, hyperpigmentation, scaling), Neurologic symptoms (somnolence, confusion, peripheral neuropathy), Hypochromic, microcytic anemia
VITAMIN B12	Megaloblastic anemia, Hypersegmented neutrophils, Cutaneous hyperpigmentation, Mucocutaneous manifestations (angular cheilitis, Hunter glossitis , localized or diffuse hair depigmentation, mucocutaneous hyperpigmentation), Neurologic signs (paresthesias, ataxia, symmetric loss of vibration and proprioception, severe weakness, spasticity, paraplegia, apathy, somnolence, irritability, memory loss, dementia)
VITAMIN C	Scurvy, Collagen defects, Defective fibroblast responses, Defective white cell production, Abnormal scar tissue formation, Impaired use of oxygen free radicals for killing bacteria, Impaired γ-globulin production
VITAMIN D	Osteomalacia, Rickets
VITAMIN E	Abetalipoproteinemia (poor transmission of nerve impulses, muscle weakness, retina degeneration), Neurolomuscolar signs (spinocerebellar ataxia, myopathies, dysarthria, absence of deep tendon reflexes, loss of vibratory sensation and proprioception), Anemia, Ocular diseases (retinopathy, cataracts), Immunosuppression, Male infertility, Dry hair or loss of hair
VITAMIN K	Multiorgan hemorrhage (cutaneous, gastrointestinal, genitourinary, and retroperitoneal bleeding), Purpura and ecchymosis, Impaired wound heeling, Immunosuppression, Neonatal vitamin K deficiency bleeding (VKDB)

secretion of sebum, follicular hyperkeratinization, bacterial colonization by Propionibacterium acnes (P. acnes), and a potent inflammatory response. Retinoids might be considered as the ideal agents for treating acne because they are able to interfere with the majority of pathogenic aspects having *(i)* anti-inflammatory effects, *(ii)* reducing seborrhea, *(iii)* regulating keratinocyte proliferation and differentiation.

Retinoids, in particular *trans*-retinoic acid (tretinoin) as topical formulation, have been used to treat acne since 1974 [21]. The principal Vitamin A metabolite used for the treatment of acne is isotretinoin (13-Cis retinoic acid). Isotretinoin regulates keratinocyte proliferation leading to a reduction of comedone formation (Table **2**). It also suppresses sebaceous-gland activity with a subsequent reduction of sebum production, which hampers *P. acnes* colonization. Because of this activity, isotretinoin is also successfully used in oral formulation for the management of severe nodulocystic acne [22-25].

Use of Retinoids in the Treatment of other Cutaneous Disorders

Vitamin A and its derivatives, etretinate and isotretinoin, have been proved effective in the treatment of keratinizing disorders such as hidradenitis suppurativa, Darier's disease, granulomatous rosacea, lamellar ichthyosis, and non-bullous congenital ichthyosiform erythroderma [26,27]. Several studies reported that oral isotretinoin might induce extended remission or cure of pityriasis rubra pilaris [28-30]. Qui vanno divise: nel punto [A] va messa la referenza 26 e 28 mentre nel punto [B] vanno messe la referenza 27, 29, e 30.

Retinoic acid and retinol are involved in the repair of photodamage by a restorative mechanism and by limiting the progression of existing damage. In particular, they inhibit the UV-induced expression of the matrix metalloproteinases, which are responsible for the breakdown of collagen fibers in the dermis. Retinoic acid regulates keratinocyte proliferation and differentiation resulting in a physiological shedding of mature keratinocytes and in smoother skin-surface texture. Moreover, it stimulates fibroblasts in producing abundant collagen, which reconstitutes regular dermal thickness and more resistance to trauma [14,15].

Regarding pigmentation, retinoids also inhibit UV-induced alterations constituted by brownish spots and overall uneven pigmentation.

Table 2: Functions and Effects of Vitamins on Skin Physiology

Effects of vitamins on cutaneous physiologic processes	
VITAMIN A	- anti-inflammatory effects - reduction of seborrhea - regulation of keratinocyte proliferation and differentiation - inhibition the UV-induced expression of the matrix metalloproteinases - promotion natural reparative processes in photodamaged skin
BETA CAROTENE	- protection cell membranes from lipid peroxidation process - inhibition of apoptosis
VITAMINA B COMPLEX: VIT. B1 (THIAMIN), VIT. B2 (RIBOFLAVIN), VIT. B3 (NIACIN), VIT. B6	- metabolic and oxidation-reduction reactions - stabilization and protection of cell membrane
VITAMIN C	- protection against UV-induced DNA damage and lipid peroxidation - formation of stratum corneum barrier lipids - normalization of epidermal lipid formation - regulation of collagen production, fibroblast responses and white cell production (scar tissue formation) - defense against infection (boosting immune response)
VITAMIN D	- inhibition of keratinocyte proliferation - induction of keratinocyte differentiation - modulation of the cutaneous immune system
VITAMIN E	- anti-inflammatory action - protection from UV light-induced long-term damages - reduction of sebum production in seborrheic skin - regulation of scar tissue formation (accelerating wound healing)
VITAMIN K	- wound healing process - defense against pathogens

Tretinoin was proved effective in ameliorating photo-induced damaging in experimental models, reflecting the efficacy of topical tretinoin in promoting natural reparative processes in photodamaged skin [31-33].

Striae, or stretch marks, can be treated with all-trans retinoic acid, which may fully or partially reverse the progression of stretch marks and decrease their length and width in 80% of patients. [17,18].

Cellulitis is characterized by areas of irregular contours with round depressions, often described as orange-peel or dimpled skin. This aspect is the result of irregular fat aggregates and both lymphatic-and connective-tissue anomalies. Retinol has been reported to improve this cosmetic defect [19]

Synthetic retinoids such as tretinoin, isotretinoin, and etretinate have been studied in many premalignant and malignant skin conditions, such as actinic keratoses, squamous cell carcinomas, Bowen's disease, basal cell carcinomas, keratoacanthomas, porokeratoses, epidermo dysplasia verruciformis, oral leukoplakia, melanoma, and cutaneous T-cell lymphomas. In these conditions, treatment with retinoids has not a therapeutic value, but may prevent the formation of new lesions as long as therapy is prescribed. Lippman *et al.* reported a complete or partial response to oral retinoids in 51% of patients affected by basal cell carcinoma, in 71% of patients presenting advanced squamous cell carcinoma [34]. Moreover, daily administration of etretinate 0.5 to 1 mg kg^{-1} was proven effective in inducing complete regression of actinic keratoses [35]. Other studies showed that high-dose of oral isotretinoin (2 mg/kg/day) decreased the yearly incidence of new basal and squamous cell carcinomas in 5 patients affected by xeroderma pigmentosum [36,37].

Vitamin A plays a relevant role in facilitating wound healing, in particular it seems to rescue the impairment of the regenerating process caused by corticosteroids and other medications. Vitamin A may enhance wound healing by participating in glycoprotein and glycolipid synthesis, prostaglandin production, and cell membrane metabolism. It also appears to influence

dermal growth by inhibiting collagenase. Conversely, vitamin A deficiency delays collagen synthesis and re-epithelialization, decreases collagen stability, and increases susceptibility to infection [20,38].

Treatment of Psoriasis with Retinoids

Topical and systemic vitamin A derivatives are highly effective in the treatment of psoriasis. Retinoids may inhibit the growth of proliferating keratinocytes and induce their terminal differentiation. The effectiveness of topical and systemic vitamin A analogues in psoriasis is well known: tazarotene 0.05% and 0.1% gels are effective in treating mild to moderate plaque psoriasis not exceeding 20% of total body surface area. Side effects include mild to moderate local irritation, pruritus, burning, or erythema. Acitretin at the dosage of 0.5 to 1.0 mg/kg/day is considered the retinoid of choice in the treatment of pustular psoriasis, but the potential occurrence of adverse events such as hair loss, hypertriglyceridemia, hyperostosis, tissue calcification, xerosis, and teratogenicity, represent a significant issue to its use [39-44].

VITAMIN B COMPLEX

Vitamin B complex consists of eight water-soluble vitamins found in meat, dairy products, vegetables, fish, brewer's yeast (beer), and cereals. Main functions performed by this group of vitamins act on cell proliferation, promoting muscle tone, immune balance and maintaining a normal functionality of the nervous system [45,46].

Vitamin B1 (thiamin)

Thiamine (aneurine) is a coenzyme involved in oxidative decarboxylation reactions and transketolation (Table **2**).

Its deficiency leads to "beriberi" disease and it is due to chronic alcoholism, hypovitaminosis, malabsorption, thyrotoxicosis, and rarely it might be correlated to thiaminase activity, an enzyme-catabolizing thiamine, especially found in raw fish (Table **1**). This condition is characterized by severe neurological and cardiovascular diseases associated to skin manifestations. An increased rate of seborrheic dermatitis-like lesions was observed in patients affected by beriberi, whereas aenterohepatica acrodermatitis-like (pluriorificial) dermatitis was correlated with amblyopia and peripheral neuritis [47].

Deficiencies of thiamine can also compromise and reduce the normal wound healing process, resulting in a decreased breaking resistance [48].

Vitamin B2 (riboflavin)

Riboflavinis are mainly found as coenzymes flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), while a small percentage is represented as free riboflavin. Riboflavin plays a pivotal role as cofactor in metabolic and oxidation-reduction reactions. Furthermore, it is also involved in vitamin B6 metabolism.

Milk, dairy products, fatty fish, eggs, green leafy vegetables, whole grains, and enriched breads are rich in riboflavin. The recommended daily intake ranges from 0.3 to 1.6 mg, depending on age and gender [49].

Patients with riboflavin deficiency (also known as ariboflavinosis) show a deep erythema, mucositis, and in some cases, epidermal necrolysis. The severity of these symptoms are correlated to the deficiency degree.

Chronic manifestations of riboflavin deficiency are described as oro-oculo-genital syndrome. It begins with small papules in the corner of the mouth, which increase in size and bleed (angular stomatitis). Cheilitis, erythema, xerosis, and cracking of the lips are frequently associated. Glossitis with hyperplasia of the lingual papillae may occur and become chronic, resulting in a smooth and magenta-colored tongue. A facial seborrheic dermatitis-like eruption form might also appear.

Scrotal dermatitis, ocular manifestations includephotophobia, conjunctivitis, and corneal vascularization represent other manifestations of ariboflavinosis, though less frequent [50].

The skin symptoms of hypovitaminosis B2 are similar to the symptoms correlated to B6 deficiency, but also to deficiency of niacin, essential fatty acids, and in cases of acrodermatitis enterohepatica (zinc-deficiency syndrome), and glucagonoma [47].

Vitamin B3 (niacin)

Niacin (nicotinic acid o vitamin B3) and its converted form, nicotinamide adenine dinucleotide (NAD) and nicotinamide adeninedinucleotide phosphate (NADPH), are important cofactors in a variety of oxido-reductases reactions.

Meat, poultry, nuts, eggs, fish, dry beans, coffee and fortified grains are dietary sources of NAD and NADPH. They are hydrolyzed to nicotinamide in the intestinal lume, where intestinal bacteria convert it into nicotinic acid and both can be so absorbed and pass into the bloodstream. They are then transported to the liver, kidneys, and again to the intestine, where they are converted back to NAD and NADPH. The recommended daily intake is 13 to 20 mg, depending on age and gender. Moreover, about half of niacin present in our organism is produced by the conversion from tryptophan, but this process requires the involvement of vitamins B2 and B6 [1,51].

The classical manifestation of niacin deficiency is pellagra, classically defined by a tetrad: dermatitis, dementia,diarrhea, and death (Table **1**).

The cutaneous manifestations can be divided into four categories: dermatitis on sun-exposed areas; perianal and genital dermatitis, lichenification and hyperpigmentation on osseous prominences, and a dermatitis mimicking seborrheic eczema [52,53].

The dermatitis is bilateral, symmetrical, and characterized, at the beginning, by a hitching, erythematosus and edematous eruption after sun exposure. By time, the eruption turns into vesicles-bullous lesions, and eventually, hyperpigmented and keratotic plaques. Cheilitis, glossitis, angular stomatitis, and oralor perirectal ulcers may be observed.

Skin symptoms are not correlated with the severity of the systemic involvement. Neurologic symptoms include headache, irritability, anxiety, hallucinations, photophobia, depression, insomnia, and impaired memory. Nausea, vomiting, abdominal pain, and diarrhea represent the most common gastrointestinal manifestations. Death occurs within 4 to 5 years in absence of treatment [53,54].

The clinical symptoms of pellagra are not only correlated by niacin deficiency. As previously mentioned, vitamin B3 in our body depends from both dietary sources or correlated to the metabolism of tryptophan that is controlled and regulated by vitamins B1, B2, B6 and amino acids. Hence, the lack of these nutrients can result in a deficiency of niacin. In fact symptoms similar to pellagra also occurs either in case of vitamin B2, B6, and zinc deficiency, or because of the lack of essential fatty acids, and in presence of glucagonoma [53,55].

Vitamin B6

The vitamin B6 group is represented by pyridoxine, pyridoxal, and pyridoxamine, and theirphosphates forms. Pyridoxal phosphate is a coenzyme for multiple critical enzymes. The phosphorylated form of vitamin B6 needs to be hydrolyzed by intestinal phosphatases before intestinal absorption. It is phosphorylated again in the liver and released into the blood circulation in its active forms. The recommended daily intake ranges from 0.1 to 2mg, depending on age and gender [1,55].

Vitamin B6 deficiency is uncommon but may occur in case of inadequate dietary intake, chronic alcoholism, uremia, malabsorption, hepatic cirrhosis and it might caused by therapy with isoniazid, hydralazine, cycloserine, penicillamine, and oral contraceptives. All these medications inactivate pyridoxal-5-phosphate or accelerate its excretion.

The most common skin manifestation is a seborrheic eruption localized in the facial, neck, and shoulder areas, in the perianal region, and in the perineum. Glossitis (characterized by flattening of the filiform papillae, redness, burning, and swelling of the tongue), stomatitis with ulcerations, cheilitis, aphtha, conjunctivitis, and intertrigo may occur. A pellagra-like dermatitis, somnolence, confusion, peripheral neuropathy, hypochromic and microcytic anemia have often been reported [47,55,56]

Vitamin B12

Cobalamin (vitamin B12) is another important coenzyme found in animal products, particularly liver, eggs, milk, and beef are rich sources of cobalamin [57].

After ingestion, gastric acid releases vitamin B12 and so it can bind to the intrinsic factor. Specific receptors take up the vitamin B12-intrinsic factor complex in the terminal ileum. After the dissociation from the intrinsic factor, Vitamin B12 reaches the portal circulation to be delivered to target tissues [58].

Causes of vitamin B12 deficiency are: decreased gastric acid secretion, decreased intrinsic factor production, microbial competition in the gut, or impaired absorption. The primary manifestation of a vitamin B12 deficiency is the megaloblastic anemia and the presence of hypersegmented neutrophils [59].

Cutaneous hyperpigmentation (diffuse or localized) might occur and it commonly affects hands, nails, face,

palmar creases, flexural regions, and pressure points [60].

Mucocutaneous manifestations include angular cheilitis, Hunter glossitis (characterized by atrophic, red, and painful tongue, with atrophy of the filiform papillae), localized or diffuse hair depigmentation, and mucocutaneous hyperpigmentation [61].

Symptoms include generalized weakness with paresthesia that progress to ataxia and symmetric loss of vibration perception and proprioception, which is more severe at lower extremities [62]. Other neurologic findings include apathy, somnolence, irritability, memoryloss, dementia, and psychosis [63].

By highlighting the immunomodulatory effects of vitamin B12 on T lymphocytes and cytokines, studies propone that vitamin B12 may be implicated in the pathogensis of psoriasis on account of its role in nucleic acid synthesis [64,65].

Studies have recently started to examine the potential use of vitamin B12 in psoriasis therapy for patients demonstrating low levels of this vitamin in psoriatic plaques, and thus far, efficacy has been established with both intramuscular and systemic vitamin B12 [66-68]. Additional research has also verified the benefit of topical vitamin B12. A randomized, prospective clinical trial evaluated the effects of topical calcipotriol cream vs vitamin B12 cream (700 mg/kg methyl glycoside stearate) containing avocado oil (containing 82.9 mg/kg vitamin E, α-tocopherol) applied twice daily for 12 weeks in thirteen patients with chronic plaque psoriasis. Use of both creams resulted in a statistically significant improvement in the PASI score. Though the beneficial effects in the vitamin B12 group were slower to develop, by week 12, the two groups expressed no notable differences in PASI scores [69].

Vitamin C

Vitamin C (L-ascorbicacid) is a water-soluble molecule with a multitude of roles. Primarily, it acts as an essential cofactor for enzymes involved in carnitine synthesis and in collagen formation. Because of the role it plays in balancing calcium metabolism, it consequently aids osteoblast formation of bone and osteodentin formation of teeth. Vitamin C, furthermore, is involved in the synthesis of catecholamines (e.g., dopamine and norepinephrine), and increases dietary iron absorption by reducing iron from its ferric to ferrous state [70]. As an antioxidant, it boosts cellular protection against UV-induced DNA damage and lipid peroxidation, in addition to increase the immune response [71-75].

Finally, vitamin C participates in the formation of stratum corneum barrier lipids as it normalizes epidermal lipid formation, including glucosphingolipids and ceramides [76].

Humans are unable to synthesize vitamin C and are totally dependent on diet. Vitamin C can be found in strawberries, green leafy vegetables, citrus fruits, berries, cantaloupes, tomatoes, potatoes and herbs [70].

Vitamin C is absorbed in the first two-thirds of the small intestine, it is not stored but renally reabsorbed. The recommended daily intake depends on age and gender, ranging from 40 to 120 mg. [58].

Vitamin C deficiency is associated with collagen defects, defective fibroblast responses and white cell production, abnormal scar tissue formation, impaired use of oxygen free radicals for killing bacteria, and γ-globulin production [77-81].

Scurvy is the classical manifestation of vitamin C deficiency (Table 1). Fresh citrus fruits were identified in the past as a treatment and prevention of ascorbic acid deficiency [82]. Sailors were frequently affected of scurvy, which represented the most likely cause of death of a sailor's voyage [83].

Scurvy is characterized by fatigue, malaise, and lethargy. Skin signs are represented by enlarged, hyperkeratotic hair follicles on the posterolateral parts of the arms, on the buttocks and legs, associated with an abnormal hair development, coiled (corkscrew) hair, “swanneck” hair, woody edema of the legs [84]. Oral manifestations are edematous, friable, erythematous and bleeding gingiva, with prominent red, smooth, swollen masses in the interdentate papillae; teeth are prone to infection [85,86]. Xerostomia, keratoconjunctivitis sicca, and salivary glands hyperplasia might occur, mimicking Sjögren syndrome [87].

Other symptoms reflecting the fragility of blood vessel walls are conjunctival and intraocular hemorrhage, gastrointestinal bleeding, anemia, folate deficiency, and iron deficiency [88-89].

Despite the promising findings from *in vitro* and experimental studies that suggest a protective role of

vitamin C in NMSC risk, though data from the literature are contradictory [90-98].

Role of vitamin C in wound healing process is also controversial because evidence does not unanimously show its positive effect in promoting healing processes [79-81,99-102].

Ascorbic acid is commonly used in a number of cosmetic products claiming to protect the skin from environmental insults and photoaging [93, 103-105].

Vitamin D

Vitamin D is a fat-soluble vitamin that can be obtained through dietary sources as ergocalciferol (vitamin D2) or endogenous synthesis as cholecalciferol (vitamin D3). It is found naturally in fish and fish oils, having the greatest amount of vitamin D available in raw natural products, but also liver, egg yolk, cheese, and mushrooms may represent alternative sources for vitamin D [106]. Clearly, it could be also found as an additive in fortified milk and cereal, or as a dietary supplement. The daily recommended intake is 200 IU from birth to 50 years, 400 IU from 51 to 70 years, and 600 IU for 71 years and older [107].

After intestinal absorption, ergocalciferol is converted, by vitamin D 25-hydroxylase, into 25-hydroxyvitamin D (calcidiol) within the liver, and released into the circulation. Through the blood vessel system, it reaches the kidney, where it is transformed to its active form, 1,25-dihydroxyvitamin D (calcitriol) [108].

However, the eighty percent of the human vitamin D synthesis begins within the skin, where the process of photoisomerization of 7-dehydrocholesterol to previtamin D3 occurs. Epidermal keratinocytes and dermal fibroblasts require ultraviolet B light in the range of 290- to 315-nm for the production of Vitamin D. Pre-vitamin D3 is transported to the liver and kidney and is converted to 1,25-dihydroxyvitamin D by the same pool enzymes implicated into the process for dietary vitamin D [109-110].

Vitamin D is essential for regulation of calcium and phosphorous metabolisms, in fact, it activates bone osteoclasts in mobilizing calcium and phosphorus, and stimulates enterocyte calcium channel synthesis in order to enhance calcium absorption [108,111,112]. Together with the relevant role of in calcium homeostasis and bone metabolism, vitamin D seems to be involved in the physiologic metabolism of other tissues and organs including the adipose tissue, kidney, endocrine and cardiovascular systems. There are conflicting data about the correlation between low levels or deficiency of vitamin D and the onset of type II diabetes, insulin resistance, obesity, metabolic syndrome, hypertension, dyslipidemia, and cardiovascular diseases. [113-121]

Albeit a statistical correlation has been found, controversial evidence about an eventual causality of vitamin D deficiency in inducing obesity has been reported: in fact, some authors suggested low levels of 25(OH)D as predisposing factor for obesity or insulin resistance, but in obese patients low vit. D levels can be likely attributed mainly to its sequestration by adiposity, poor vitamin intake, limited sun exposure, and reduced bioavailability. [122-124]

Skin cells, including keratinocytes, Langerhans cells, melanocytes, fibroblasts, dermal dendritic cells, B and T cells, and endothelial cells, express vitamin D nuclear receptor. The activation of this receptor, when it is bound to vitamin D and its analogs, leads to: *(i)* the inhibition of the keratinocyte proliferation; *(ii)* promotion of both *in vitro* and *in vivo* keratinocyte differentiation; and *(iii)* regulation of the cutaneous immune system, antiproliferative and proapoptotic effects (Table 2) [125-127].

Overall these multiple effects contribute to the therapeutic success of this class of molecules in the treatment of psoriasis [128-132].

The effect of oral 1,25-(OH)2-D3 in the treatment of psoriasis was proven effective though it might be associated with the occurrence of adverse events such as hypercalcemia, hypercalciuria, nephrocalcinosis, nephrolithiasis, and reduction in bone mineral density. Initial clinical experience with oral vitamin D3 showed a potential benefit for the treatment of psoriasis [133-134]. A small prospective study was conducted on 17 patients with moderate to severe psoriasis treated with either oral or topical 1,25-(OH)2-D3, starting with a dose of 0.25 µg once or twice daily. Thereafter, dosing was increased as long as urinary calcium levels remained within the normal range. During the study, it was observed that a single dose at bedtime, rather than twice daily, helped to minimize the hypercalciuria. Of the 14 patients, ten showed a “significant clearing,” whereas 4 patients had no benefit or only mild clinical response [135].

A 6-month, pilot study testing daily oral 1,25-(OH)2-D3 administration in patients affected psoriatic arthritis

showed at least moderate improvement for 7 of 10 patients. Four of nine patients evaluated for their skin lesions experienced a marked improvement, whereas a worsening of the psoriatic plaques was observed in two patients [136]. Similarly, another trial showed that oral 1,25-(OH)2-D3 at 0.5 to 2 μg/day prescribed for 6 months, induced at least a moderate response in skin lesions in two of eight enrolled patients [137].

Because of its immunomodulatory effect, vitamin D has also been used to treat inflammatory diseases. The therapeutic efficacy of oral calcitriol and calcipotriene in the treatment of morphea has been well reported [138,139]. Based on this result, the efficacy of vitamin D has been proved in the treatment of lichen sclerosus. A specific mechanism of action has not fully understood, but a number of case reports documented the effectiveness of topical calcipotriene on extragenital lichen sclerosus [140-143].

Several studies investigated the use of vitamin D and its analogues as chemoprevention for melanoma and metastasis of malignant tumors. The association between high levels of 25-hydroxyvitamin D3 and low melanoma lesion thickness at the time of diagnosis was observed in two different studies [144,145].

A large cohort of 70000 patients affected by melanoma, on the contrary, did not demonstrate the existence of a relationship between melanoma incidence and vitamin D intake [146]. This result could be probably explained by varying susceptibilities to melanoma based on various vitamin D receptor gene polymorphisms [145]. Nevertheless, vitamin D may still be important in melanoma chemoprevention in some individuals.

In vitro studies suggested an association between vitamin D and non-melanoma skin cancers (NMSC), because of the vitamin D interaction with intranuclear vitamin D receptors (VDRs), expressed in keratinocytes [147-150].

Unfortunately, clinical data concerning the potential benefit of vitamin D on NMSC are lacking. The effect of topical calcipotriol (6-week application) on actinic keratoses (AKs) resulted poor [151]. On the contrary showed that 12-week application of topical calcipotriol significantly ameliorated AKs, compared with application of placebo [152]. Other studies failed to show an association between vitamin D and BCCs [153-155].

Vitamin E

Vitamin E includes eight naturally occurring forms of a fat-soluble antioxidant (α-, β-, γ-, and δ-tocopherols and tocotrienols) that are present in vegetables, oils, seeds, corn, soy, whole wheat flour, margarine, nuts, some meats, asparagus, avocado, eggs, seeds, nuts, spinach, and some dairy products [156,157].

Vitamin E, as an intracellular antioxidant, protects cell membrane from a wide spectrum of free radicals including singletoxygen, superoxide, and hydroxyl radicals, and it is fundamental as a chain-breaking antioxidant during lipid peroxidation in membranes [156,158-160].

In relation to its anti-inflammatory action, vitamin E has been used for various dermatological conditions: as skin protector for acute and chronic dermatitis, sunburn, and UV light-induced long-term damages (Table **2**) [161-171]. It also seems to be effective in *(i)* reducing sebum production in seborrheic skin [172], *(ii)* promoting hair growth possibly increasing microcirculation [173], *(iii)* decreasing pruritus [174,175], *(iv)* accelerating wound healing [176-179], and *(v)* protecting from hypertrophic scar formation (Table 2) [180-183].

The effects of oral and topical vitamin E on skin photoaging effects, skin cancer formation, sunburn prevention need to be defined [162-171, 184-190].

Interestingly, studies on elderly population indicate a lower incidence of infectious disease and cancer in subjects maintaining high plasma tocopherol levels [191-194].

Several authors reported the satisfactory use of vitamin E as co-adjuvant in various inflammatory conditions of the skin such as discoid lupus erythematosus and lichen sclerosus et atrophicus [195-199].

The yellow nail syndrome, an uncommon condition associated with lymphatic obstruction and pleural effusions, could be treated with vitamin E [200,201]. The peculiar yellow coloration is due to the presence of the lipofuscin, derived from lipid oxidation [202]. Through its antioxidant effect, vitamin E may inhibit the pigment production [200].

Vitamin K

Vitamin K belongs to a group of fat-soluble vitamins, occurring asphylloquinone (vitamin K1) in green leafy

vegetables, liver, Brussels sprouts, lentils, plant oils, and soybeans. It is absorbed in the uppersmall intestine, where gastrointestinal bacteria synthesize approximately 50% of daily vitamin K (asmenaquinone, vitamin K2). Recommended daily intake of vitamin K ranges from 2 to 120 µg, similarly for age and gender [203].

Vitamin K is involved in bone metabolism and is essential for synthesis of several coagulation factors such as factor II, factor VII, factor IX, factor X, protein C, and protein S [203-206].

Vitamin K deficiency impairs coagulation cascade resulting in hemorrhagic events (i.e., cutaneous, gastrointestinal, genitourinary, and retroperitoneal bleeding), purpura, and ecchymosis [206-210] Furthermore, alteration of multiple biologic processes including wound repair, host defense against infection is common in vitamin K deficiency [211, 212]

CONCLUSION

The therapeutic approach in skin disorders has profoundly changed in the last few decades. Vitamins represent a relevant class of therapeutic agents and co-adjuvants in the management of cutaneous diseases. Due to their antioxidant effects, vitamins might constitute an important support to conventional drugs and to chronic inflammatory state, and their cosmetic effects might represent a useful tool for various disorders.

Vitamin A and vitamin D derivates that successfully act on specific pathological aspects of common inflammatory skin diseases such as acne and psoriasis represent two principal examples of the significant contribution of vitamins in skin therapy.

The role of vitamins in the management of skin disorders is often underestimated, and though further investigations are necessary to explore their potentiality, their use would propone a therapeutic alternative whose health benefits extend beyond the realm of skin disease.

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