Vitamin B group levels and supplementations in dermatology

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Abstract

Irregularities of vitamin levels are being increasingly identified associated with skin conditions, and systemic and topical therapies have shown promising improvements. There have been some remarkable improvements achieved, but large variations in outcomes suggest that these conditions are not simply related to a single deficiency or solved by providing a single supplement. Cyanocobalamin, pyridoxine (B6) and riboflavin (B2) supplementation were linked with exacerbating existing acne. There were also reports of allergic reactions to parenteral cobalamin including acne, rosacea, allergic site reactions or anaphylaxis with cobalamin injections. This was also reported in patients who had allergic contact dermatitis to cobalt, where cobalamin therapy resulted in cutaneous manifestations such as chronic vesicular hand dermatitis, cheilitis and stomatitis. The use of niacinamide in acne vulgaris as an alternative to clindamycin or adjunct is also notable, as well as its application for hyperpigmentation. Vitamin B3 also has promise in chemoprevention in particular non-melanoma skin cancer prophylaxis. Folic acid has a developing role in psoriasis. The data for vitiligo remains inconclusive. Assessment for potential vitamin deficiency, particularly B vitamins, should form part of the normal work-up for a wide range of skin conditions.

Introduction

Irregularities of vitamin levels are being increasingly identified associated with skin conditions, and systemic and topical therapies have shown promising improvements.

The World Health Organisation (WHO) has estimated >2 billion people globally have suboptimal intakes of some essential vitamins and minerals, and that this trend is increasing.[1] The reasons are complex, including poverty and food shortages in many countries, but also through poor diets and food choices in the developed world.[1] Unbalanced diets featuring high energy and extensively processed foods are contributing to the problems. There have also been reports that changes in farming and intensive cultivation methods has led to a reduction in vitamin content in certain foods,[2] although others have suggested that the level of reduction is more than compensated through higher yields and therefore, plentiful supply.[3] WHO further reports that in 2020, worldwide, 462 million people are underweight, but 1,9 billion are overweight or obese. Being overweight increases the risk from a range of diseases including the metabolic syndrome and type 2 diabetes mellitus.[1] These conditions and their associated complications and co-morbidities are characterised by high levels of oxidative stress. Against this background, extensive interest is focussing on the role played by vitamins and vitamin deficiencies in skin disorders.[4,5] There have been some remarkable improvements achieved, but large variations in outcomes suggest that these conditions are not simply related to a single deficiency or solved by providing a single supplement. In both cellular metabolism and in protection against oxidative stress, the roles of the B vitamins are intertwined and interdependent at the cellular level, and also linked to the effects of other vitamins. The B vitamins are listed in Table 1, although several can occur, and may be administered therapeutically, in more than one chemical form.

Vitamin B3

Vitamin B3 (niacin or nicotinic acid) can be synthesized in the body from the amino acid, tryptophan. Dietary sources are eggs, milk and legumes. In many countries, it may also be supplemented in flour. It is a key component of nicotinamide adenine dinucleatide in cellular energy production.[6] Nicotinamide is the amide derivate, also known as niacinamide. Nicotinic acid supplementation can be problematic, with severe side effects including flushing, hypotension, itching and headache. Conversely, nicotinamide has fewer side effects. The most serious of which is nausea.[7,8] Nicotinamide has various applications in dermatology and has been described as beneficial in non-melanoma skin cancer (NMSC) prophylaxis, blistering disorders, acne vulgaris and for anti-ageing cosmetic purposes.[9] Nicotinamide has been used prophylactically, both orally and topically in NMSC.[10,11] It delays immunosuppressive effects of ultraviolet radiation and hinders the oxidative stress secondary to such radiation.[12] This has promoted its application for actinic keratoses and NMSC in high-risk individuals. Nicotinamide also enhances repair of DNA damage in melanocytes so it shows promise for a role in cancer chemoprevention.[13] Nicotinamide also inhibits the proinflammatory cytokine pathways and has shown therapeutic bene-

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fits from oral use in blistering disorders, for example, bullous dermatoses.[13-15] Topical use has shown improvement in acne vulgaris,[16] because of its anti-inflammatory properties and role in the reduction of sebum production.[17] In these studies, in which an oral supplement containing nicotinamide was used, the results showed significant reduction in acne compared with baseline. Topical nicotinamide had significant benefits on reducing acne vulgaris and performed like clindamycin in 4 separate studies.[17-20] Vitamin B complex injection (each mL contains: B1 (thiamine HCl) 100 mg, B2 (riboflavin-5-phosphate sodium) 2 mg, B3 (niacinamide) 100 mg, B5 (dexpanthenol) 2 mg, B6 (pyridoxine HCl) 2 mg) has also shown a significant role in the management of phrynoderma whereby intramuscular dual therapy with safflower oil or with vitamin E improved and smoothed out the appearance of lesions.[21] Nicotinamide treatment has also shown benefit cosmetically in melasma and hyperpigmentation.[22,23] Patients likely to be deficient in niacin include those living in poverty, those with eating disorders or eating a nutritionally incomplete diet, especially high corn diets, alcohol abuse, liver cirrhosis, inflammatory bowel disease, and those with advanced AIDS.[24] Deficiency can lead to pellagra which presents with diarrhoea and a dermatitis characterised by diffuse erythema, hyperpigmentation, crusting and ulceration on sun-exposed areas of skin.[24]

Vitamin B6

Vitamin B6 (pyridoxine) is an essential cofactor in many metabolic processes including methylation, transamination, and the synthesis of neurotransmitters and haemoglobin.[25] Dietary sources of pyridoxine include meat and fish and a wide range of fruit and vegetables. Deficiency is associated with seborrheic dermatitis, cheilitis and peripheral neuropathy. Excessive supplementation has been associated with nausea and other gastrointestinal symptoms, skin eruptions, and sensory neuropathies. Deficiency is reported to be uncommon in developed countries. Risk factors for deficiency include obesity, inflammatory bowel disease, coeliac disease, chronic alcoholism, and pregnancy.[25] As noted by Coerdt,[4] seborrheic dermatitis has been associated with low B6 levels. *Ground substance* is a term used to describe the amorphous gelatinous extracellular matrix. It consists mainly of glycosaminoglycans linked with proteins to form proteoglycans.[26] The proportion of protein is small, but it has a major impact on the viscosity.[27] Low levels of pyridoxine inhibit protein metabolism leading to increased viscosity. This has been linked to increased inflammatory reactivity precipitating seborrheic dermatitis.[27] Deficiency also inhibits the activity of ornithine aminotransferase reducing the availability of proline for collagen formation. Proline deficient collagen has been linked to pellagra lesion formation.[28]

Vitamin B7

The use of vitamin B7 (biotin) is common for hair, skin and nail problems.[4] Biotin (B7) is water-soluble. It has been demonstrated to have a role as a co-factor in multiple metabolic processes including cell signalling, gene regulation, histone modification and carboxylation.[29] Certain enteric bacteria are able to synthesise biotin, but the major source for humans is protein-rich foods; egg yolks, milk, nuts and grains.[30] Lipner reported that 200 out of 300 dermatologists questioned had recommended biotin supplementation to patients to improve hair, nails and general skin health.[30] In this context, it is important to note that a possible consequence of biotin supplementation is interference with a range of laboratory tests that use immunoassay methods. High levels of biotin have been associated false negative troponin levels and false positives for streptavidin. It has also been reported to interfere with urine tests for human chorionic gonadotrophin. However, Lipner also reported that supplementation of 10 mg/day for 7 days to 6 healthy individuals produced falsely low measurements of thyroid stimulating hormone, parathyroid hormone and brain natriuretic peptide levels and falsely elevated triiodothyronine levels.[30]

Vitamin B9

Vitamin B9 folic acid is a water-soluble vitamin, essential to DNA synthesis. In 1930, Lucy Willis discovered the anti-anaemic activity. It was identified and named folic acid, from the Latin word *folium* for leaf, after it was isolated from spinach leaves.[31] Rich sources of dietary folate include green leaves, grasses, mushrooms, yeasts and animal offal (particularly liver and kidney). A proportion of daily intake also comes from the intestinal bacterial flora.[31] Deficiency is associated with macrocytic anaemia, neural tube defects in pregnancy and high plasma homocysteine levels. In dermatology, the emerging theme around folate is the role of high plasma homocysteine levels and folate acid supplementation in psoriasis.[32,33] Homocysteine is a metabolic intermediate sulphur containing amino acid. The quoted normal range for its level in plasma is 5-15 micromol/L.[34] Its removal from plasma is through several pathways; around 50% is re-methylated forming methionine through two distinct mechanisms, one of which is folate/B12 dependent as described below, and one is independent of these co-factors.[32]

The link between plasma homocysteine, folate and vitamin B12 levels was recently established in a systematic review and meta-analysis.[35] They concluded that psoriasis was associated with hyperhomocysteinaemia and with folate deficiency. Significantly higher homocysteine was found in psoriasis patients than were seen in controls. There was no significant difference in B12 levels, but folate levels were lower in psoriasis patients. However, they concluded that the benefit of folate supplementation in psoriasis has yet to be established.[35]

Vitamin B12

Vitamin B12 can be found as methyl cobalamin and adenosyl cobalamin in the body.[36] It is a water-soluble molecule synthesised in bacteria. Although human enteric bacteria are able to synthesise B12, the bacteria that produce it are located in the colon, beyond the site of B12 absorption in the terminal ileum. Dietary sources include animal livers, red meat, cheese and milk.[37] Cobalamin is a cofactor in cellular methylation processes.[38] Several dermatologic conditions including vitiligo, aphthous stomatitis, atopic dermatitis and acne have been related to cobalamin excess or deficiency. Pathological conditions where patients have cobalamin excess, such as chronic myelogenous leukaemia and hyperoesinophilic syndrome, can manifest cutaneously.[39] Hyperoesinophilic syndrome may present

Table 1. B group vitamins.

Vitamin	Scientific name
B1	Thiamine
B2	Riboflavin
B3	Niacin
B5	Pantothenic Acid
B6	Pyridoxine
B7	Biotin
B9	Folic Acid
B12	Cyanocobalamin

with eczema erythroderma, lichenification, recurrent urticaria, angioedema and mucosal ulcers.[40] Deficiency in vitamin B12 can manifest as hyperpigmentation, notably in flexural areas, palms, soles and inside the oral cavity.[41] There can also be hair and nail changes, as well as oral changes including glossitis, recurrent ulcers, dysgeusia and stomatitis.[39] Cobalamin deficiency can also be seen in patients with malabsorption, pernicious anaemia, patients with an ileocecal resection,[36] and patients receiving protracted therapy with proton-pump inhibitor medications.[42] A 2015 review of vitamin B12 explored the manifestations of vitamin B12 excess, deficiency and the mucocutaneous complications of therapy.[39]

The review included a study in India, which reported patients with cobalamin deficiency and a darker pigmentation had a higher prevalence of cutaneous manifestations.[43] It revealed skin and mucosal changes in 41% of patients. Patients had glossitis, hyperpigmentation, hair changes, angular stomatitis and vitiligo.[43] Another study, where a 1000 mcg dose of sublingual vitamin B12 was administered, showed effective treatment for recurrent aphthous stomatitis patients.[44] This was independent of the patients' serum vitamin B12 level.[44]

In a separate study, patients treated with isotretinoin for acne vulgaris were found to have cobalamin deficiency. An association with cobalamin deficiency and neuropsychiatric side effects of isotretinoin was hypothesised,[45] and requires further investigation. The review also reported the clinical benefit of topical cobalamin therapy for atopic dermatitis, where the use of 0.07% cyanocobalamin cream for 8 weeks on one side of the body showed significant improvement.[46,47] Another study supported this, with evidence of vitamin B12 derivatives to enhance skin permeability.[48] Studies which explored cobalamin deficiency and therapy for vitiligo treatment were inconclusive.[49-52]

Directions for future research

The review also highlighted some complications with cobalamin therapy. These included monomorphic acneiform eruptions in patients who received intramuscular injections, that resolved on therapy cessation.[53] Cyanocobalamin, pyridoxine (B6) and riboflavin (B2) were linked with exacerbating existing acne.[53] There were also reports of allergic reactions to parenteral cobalamin including acne, rosacea, allergic site reactions or anaphylaxis with cobalamin injections.[54] This was also reported in patients who had allergic contact dermatitis to cobalt, where cobalamin therapy resulted in cutaneous manifestations such as chronic vesicular hand dermatitis, cheilitis and stomatitis.[55] As shown above, it is clear that individual B vitamins are associated with a range of disorders of the skin, and that supplementation has been successful in improving or correcting them. However, evidence of mixed outcomes is suggesting that an approach of using single vitamins may be useful for research but sub-optimal clinically. There is growing evidence that the metabolic pathways underlying the skin manifestations reported, involve more than one vitamin at particular stages in interlinked biochemical pathways. It is suggested that this should guide the approach to treatment.

The one carbon transfer pathway is a series of metabolic pathways that are interlinked. These pathways are central to intracellular function, providing methyl groups used in the synthesis of phospholipids, amino acids, creatinine, RNA and DNA.[56] They include the folate cycle, which by definition is folate dependent but also requires pyridoxine as a co-factor.[57] Methyltetrahydrofolate also feeds into the methionine cycle, in which cobalamin is methylated to methylcobalamin as another methyl donor.[57] Another important area is antioxidant activity. Oxidative stress arises from an imbalance between reactive oxygen species (free radicals) produced as part of normal metabolism, and the antioxidant defences of normal cells.[58] It is known to form a significant part of the pathophysiology of a range of conditions including diabetes mellites, cardiovascular disease, polycystic ovarian syndrome, cancers, neurodegenerative diseases and skin conditions. Vitamins known to have antioxidative properties include vitamin A, B2, B3, B6, C, D, E and K.[59] One example of the interconnected nature of these pathways was reflected in a study using folate supplementation to reduce plasma homocysteine levels. Patients received either a control diet, control diet plus folic acid supplement or a diet enhanced with folate-rich foods. During folate supplementation, they identified a significant decrease in riboflavin status, whilst in those receiving the enhanced folate-enriched diet, riboflavin status improved.[60] Similarly, poor results from supplementation of single antioxidants in a range of conditions has prompted studies looking at using more than one simultaneously.[58,61-64] Our knowledge of the involved mechanisms, and their interconnections make this a logical approach, but such studies are difficult to design and conduct. Vitamin supplements also pose the debate as to whether a single dose, once, or even multiple times per day is an effective substitute for consuming a mix of vitamins naturally as part of a healthy diet. Despite many publications referring to supplements as a source of expensive urine, for many years supplementary tablets have corrected clinical deficiencies, but studies suggest that the overall outcomes from a healthy diet are better overall than from supplementation.[65]

Conclusions

The studies discussed vary in terms of sample size, study design, length of follow up and study demographics. Different outcome measures were used, and particularly in respect of assessment of patient satisfaction, there is considerable risk of bias.

It is important to identify muco-cutaneous features as they can help to provide an early diagnosis of vitamin B deficiency. The use of niacinamide in acne vulgaris as an alternative to clindamycin or adjunct is also notable, as well as its application for hyperpigmentation. Vitamin B3 also has promise in chemoprevention in particular non-melanoma skin cancer prophylaxis. Folic acid has a developing role in psoriasis. The data for vitiligo remains inconclusive. More research is required but multivitamin and mineral supplementation should be investigated alongside single vitamin supplements. Assessment for potential vitamin deficiency, particularly B vitamins, should form part of the normal work-up for a wide range of skin conditions.

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