Review Article

Diet in dermatology: Revisited

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DOI: 10.4103/0378-6323.60540

ABSTRACT

Diet has an important role to play in many skin disorders, and dermatologists are frequently faced with the difficulty of separating myth from fact when it comes to dietary advice for their patients. Patients in India are often anxious about what foods to consume, and what to avoid, in the hope that, no matter how impractical or difficult this may be, following this dictum will cure their disease. There are certain disorders where one or more components in food are central to the pathogenesis, e.g. dermatitis herpetiformis, wherein dietary restrictions constitute the cornerstone of treatment. A brief list, although not comprehensive, of other disorders where diet may have a role to play includes atopic dermatitis, acne vulgaris, psoriasis vulgaris, pemphigus, urticaria, pruritus, allergic contact dermatitis, fish odor syndrome, toxic oil syndrome, fixed drug eruption, genetic and metabolic disorders (phenylketonuria, tyrosinemia, homocystinuria, galactosemia, Refsum's disease, G_6PD deficiency, xanthomas, gout and porphyria), nutritional deficiency disorders (kwashiorkar, marasmus, phrynoderma, pellagra, scurvy, acrodermatitis enteropathica, carotenemia and lycopenemia) and miscellaneous disorders such as vitiligo, aphthous ulcers, cutaneous vasculitis and telogen effluvium. From a practical point of view, it will be useful for the dermatologist to keep some dietary information handy to deal with the occasional patient who does not seem to respond in spite of the best, scientific and evidence-based therapy.

Key words: Diet, dermatology, nutrition

INTRODUCTION

Diet has a unique place in dermatology, particularly in a country like India, where most people are convinced that their skin condition is intimately connected to their dietary habits and will improve on modifying the same. They may not be entirely wrong in this belief, considering the fact that many alternative systems of medicine in India, and in other parts of the world, do rely on dietary modifications to deal with commonly encountered disorders. The word diet itself is derived from the Latin word *diaeta*, meaning "prescribed way of life," and from the Greek word *diaita,* meaning "way of life, regimen, dwelling."[1]

The classical dermatologic disorder where diet has a role to play is dermatitis herpetiformis. There are a number of other skin conditions where diet may have a role to play and these may be classified as follows:

1. **Dermatologic disorders in which diet has a definite role**
   Dermatitis herpetiformis
2. **Dermatologic disorders in which diet has a probable role in etiopathogenesis**
   Atopic dermatitis
   Acne vulgaris
   Psoriasis vulgaris
   Pemphigus
   Urticaria
   Pruritus
   Allergic contact dermatitis
3. **Dermatologic disorders in which specific factors in the diet are directly implicated in the etiopathogenesis of the disorder**
   Fish odor syndrome
   Toxic oil syndrome
   Fixed drug eruption
4. **Genetic and metabolic disorders wherein either an elimination diet is mandatory or dietary supplementation of specific factors is beneficial**
   Phenylketonuria
   Tyrosinemia
   Homocystinuria
   Galactosemia
   Refsum's disease

How to cite this article: Kaimal S, Thappa DM. Diet in dermatology: Revisited. Indian J Dermatol Venereol Leprol 2010;76:103-15.
Received: January, 2009. **Accepted:** April, 2009. **Source of Support:** Nil. **Conflict of Interest:** None declared.

G_6PD deficiency
Xanthomas
Gout
Porphyria

5. **Disorders related to deficiency or excess of specific nutrients**
   Kwashiorkar
   Marasmus
   Phrynoderma
   Pellagra
   Scurvy
   Acrodermatitis enteropathica
   Carotenemia
   Lycopenemia
6. **Miscellaneous disorders with an uncertain relationship to diet**
   Rosacea
   Vitiligo
   Aphthous ulcers
   Cutaneous vasculitis
   Telogen effluvium

DERMATITIS HERPETIFORMIS (DH)

A gluten-free diet (GFD) is the mainstay of treatment in celiac disease.[2] It alleviates gastrointestinal symptoms much more rapidly than the rash. The rash of DH is gluten-dependent and there are several advantages to a GFD in the management of DH. After following 133 DH patients who consumed a GFD, Garioch *et al.*[3] reported that the related advantages are (1) the need for medication is reduced or abolished, (2) there is resolution of enteropathy, (3) a general feeling of well-being and (4) protective effect against development of lymphoma. Patients with DH often have malabsorption. A GFD improves absorption of essential nutrients and prevents alimentary deficiencies of iron, vitamin B12 and folate.[2] Patients without gastrointestinal symptoms often report a general feeling of well-being on commencement of the GFD.[2] The increased risk of developing lymphoma in the gastrointestinal tract may be due to polyclonal stimulation of lymphocytes, by gluten, giving rise to malignant transformation. Several studies have demonstrated a protective effect of a GFD against the development of lymphoma.[3] In one study, lymphomas occurred in eight of 487 patients with DH and all lymphomas occurred in patients whose DH had been controlled without a GFD or in those who had been treated with a GFD for less than 5 years.[4]

Foodstuffs containing gluten, and hence to be avoided, are wheat, rye, oats and barley. Rice, corn and potatoes are safe for consumption. Iodine-containing food (fish, kelp, iodized salt and vitamin) may be avoided in patients who do not respond to a GFD, as iodides worsen DH by local chemotaxis and stimulating neutrophil migration.[5]

ATOPIC DERMATITIS (AD)

Role of diet in AD

The role of diet in the cause and treatment of AD is very controversial. Pediatricians and allergologists are convinced of the causative role of food in the onset of AD, while dermatologists are convinced of the contrary.[6] Arguments in favor of the role of diet in AD include the fact that some foods provoke AD, an elimination diet can heal AD, diet manipulation can prevent allergy in newborns at risk for atopy, presence of specific serum immunoglobulin (Ig) E for food allergens (positive radioallergosorbent test [RAST]), positive prick tests to foods and the presence of intestinal mast cell degranulation and IgE, tumor necrosis factor (TNF)-α, eosinophil chemotactic protein and alpha-1 antitrypsin (α1-AT) in the feces. The corresponding arguments against the hypothesis that foods aggravate AD are the fact that AD can persist despite elimination diets and diet manipulation can delay but not prevent allergy in newborns at risk for atopy, positive RAST and prick test results may be irrelevant or unrelated to AD and gastrointestinal symptoms are absent in spite of the presence of various proinflammatory cytokines in the feces.[6]

The mechanisms of aggravation of AD by food are:

- Increased binding of antigen to immature gut microvillus, along with increased intestinal permeability in small children (and AD), can initiate and perpetuate prompt immune responses in atopic patients with primarily altered antigen transfer.[7]
- The role of pathogenic bacteria in the gut may be similar to the role of *Staphylococcus aureus* in the skin of AD patients, both as an infectious agent as well as a super antigen.[8]

Clinical features of food allergy

Clinical manifestations of food allergy can remain localized at the site of the primary direct contact, i.e. the oropharynx (oral allergy syndrome) or the gastrointestinal tract (isolated gastrointestinal food allergy); however, after ingestion, resorption and hematogenous transport of food allergens to the various

target organs, other symptoms can occur. The skin is the most frequently affected organ. The spectrum of cutaneous adverse reactions to food includes urticaria and angioedema, induction or flare of AD, contact urticaria, protein contact dermatitis and allergic contact dermatitis. Non-dermatologic manifestations of food allergy include vomiting, diarrhea, abdominal pain, rhinitis, asthma and, also, anaphylaxis.[9]

The most common manifestation is acute urticaria (with or without angioedema), accounting for 40–60% of patients with IgE-mediated food allergy. In the case of pruritus, erythema or urticaria, the subsequent scratching can worsen the skin conditions and exacerbate pre-existing AD (dual reaction). Worsening of the eczema occurring 6–48 h after food provocation without an immediate reaction is rarely observed (late reaction). The pathogenesis of such late reactions is unclear. Among the mechanisms discussed are a late phase, IgE-dependent mechanism with formation of leukotrienes and other substances of the arachidonic acid cascade, a type III reaction with circulating IgE or IgG immune complexes that activate the complement system and delayed-type hypersensitivity mediated by T cells and activated eosinophils.[9] The role of food allergy in the pathogenesis of AD is still controversial; however, there is no doubt that, particularly in infants and young children, food allergens can induce AD or aggravate skin lesions. In adults, food allergy as a cause or a trigger of AD is very rare. However, in food-allergic patients with AD, the ingestion of the food item can provoke the whole spectrum of IgE-mediated symptoms, from oral allergy syndrome to severe anaphylaxis.[9]

Food allergy plays a role in 20% of children under the age of 4 years with AD. A direct effect on eczema is observed in four of 10 children with AD and proven food allergy.[10] Ninety percent of food allergy is caused by six foods such as wheat, milk, soy, fish, eggs and peanut.[11]

Evaluation of food hypersensitivity

It is very important to use appropriate procedures to evaluate food hypersensitivity. Misdiagnosis of food allergy and implementation of highly restrictive diets can lead to severe malnutrition. The methods of testing to confirm food allergy are the skin prick test, skin application food test (SAFT), RAST and the oral challenge test. The skin prick test is the test of first choice for investigating immediate IgE-mediated reaction. The SAFT has been developed by Oranje *et al.* on the basis of the mechanism of the contact urticaria syndrome.[12] In the SAFT test, the food, in the same state as it is consumed, is applied on the back of the patients using large Finn chambers and the test is read after 10, 20 and 30 mins. Skin tests may be performed with commercially available extracts of foods or fresh foods, although fresh foods give a better result and are preferred. Ideal and final proof of the diagnosis of food allergy is obtained only by (double-blind and placebo-controlled) oral challenge. However, the SAFT is a reliable and child-friendly skin test for evaluating (suspected) food allergy in children younger than 4 years with AD.[13]

Dietary interventions in AD

A recent Cochrane review of nine randomized controlled trials of food allergy in patients with AD showed that there appears to be no benefit of an egg and milk-free diet in unselected participants with atopic eczema.[14]

There appears to be little benefit in eliminating cow's milk from the diet or using an 'elemental' (liquid diet containing only amino acids, carbohydrates, fat, minerals and vitamins) or 'few foods diet' for improving atopic eczema in people who have not undergone any form of testing (for specific IgE to food allergens). There may be some benefit in using an egg-free diet in infants with suspected egg allergy who have positive specific IgE to eggs. This is important, particularly since some children with AD show impaired physical development, secondary to gastrointestinal involvement. Although strict elimination diets may be impractical, there is evidence to show that a strict antigen avoidance regimen may be associated with improvement of refractory widespread AD where conventional treatments have failed.[15] Having said this, it must be remembered that a very strict diet can lead to nutritional deficiency.

With regard to preventive diets, high-risk infants may benefit from maternal diet during lactation, although there is no documented beneficial effect of maternal diet during pregnancy.[10]

Treatment of AD can be supported by supplementation of 'probiotic' intestinal bacteria.[16] A probiotic is currently defined as a live microbial food supplement with an established beneficial effect on human health.[17]

Probiotics are selected from members of the normal healthy intestinal microbiota, most of them belonging to Lactobacillus or Bifidobacterium. The aims of intervention are to avert deviant microbe development, strengthen the immature or impaired gut barrier function and alleviate abnormal immune responsiveness. However, a recent Cochrane Intervention Review suggests that probiotics are not an effective treatment for eczema and may, in fact, carry a small risk of adverse events such as infections and bowel ischemia.[18]

ACNE

The general view held by modern-day dermatologists with regard to diet and acne is that diet is unrelated to the etiopathogenesis of acne. Unfortunately, there is little substantive evidence in the historical literature that conclusively supports or refutes this view. The relationship of acne to foods is certainly not new. The major US textbooks of dermatology, popular in the early 1950s, contained elaborate prose regarding specific foods to avoid.[19] The admonition to avoid chocolate, fats, sweets and carbonated beverages was commonly given to patients as part of acne therapy. But, all of this dietary advice has been removed from standard texts[20,21] and it has been many years since restriction of specific foods has been recommended in managing acne. There is the occasional patient who insists that his or her acne is exacerbated by a certain food item and it is noteworthy that 30% of medical students surveyed in Australia believed that acne is influenced by diet.[21]

There are a number of recent articles that have reexamined the role of diet in acne. Acne has been reported to be absent in non-westernized populations such as the Inuit (i.e., Eskimo), Okinawa islanders, Ache hunter-gatherers and Kitavan islanders.[23] Although familial studies have demonstrated that hereditary factors are important in determining susceptibility to acne, the complete absence of this disease in non-westernized populations points strongly to underlying environmental factors, including diet.[24] A MEDLINE search revealed that, since 1971, no single human study has been published examining the role of diet in the etiology of acne.[25]

The four main pathogenetic factors in acne are believed to be (1) increased proliferation of basal keratinocytes within the pilosebaceous duct along with incomplete separation of ductal corneocytes from one another via impairment of apoptosis and subsequent obstruction of the pilosebaceous duct, (2) androgen-mediated increases in sebum production, (3) colonization of the comedo by *Propionibacterium acnes* and (4) inflammation, both within and adjacent to the comedo.[26]

The influence of diet on acne may be discussed with respect to three of the above factors:

Keratinocyte proliferation and corneocyte desquamation

Chronic consumption of high glycemic load carbohydrates may cause long-term hyperinsulinemia and insulin resistance.[23,24] Insulin influences circulating concentrations of free insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3), which in turn directly regulate keratinocyte proliferation and apoptosis. Hyperinsulinemia in turn may initiate an endocrine cascade that affects the sebaceous gland and follicular keratinization and involves IGF, IGFBP-3, androgens and retinoid signaling pathways. The development of hyperinsulinemia and insulin resistance also elicits a pathological rise in serum concentrations of non-esterified free fatty acids (NEFAs), which in turn has been shown to cause an overexpression of the epidermal growth factor receptor [Figure 1].

A low glycemic load diet has been shown to be beneficial in patients with acne vulgaris. The glycemic load for a particular food is calculated as (Glycemic index for food item x its carbohydrate content in grams/100).[27]

Androgen-mediated sebum production

Hyperinsulinemia may promote acne by its well-

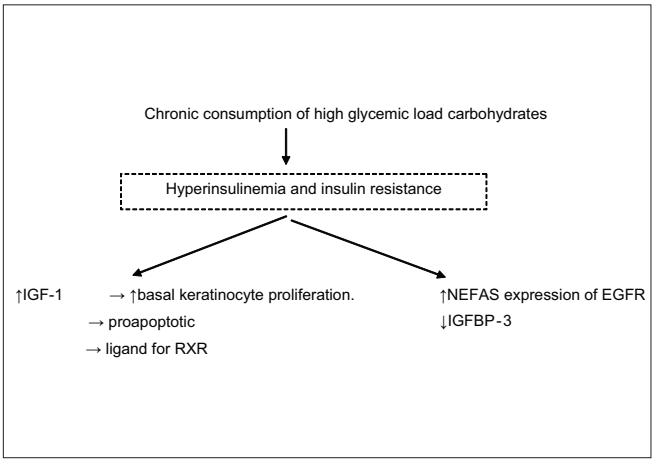

Figure 1: Role of glycemic diet in acne

established androgenic effect.[24] Both insulin and IGF-1 stimulate the synthesis of androgens in ovarian and testicular tissues. Further, insulin and IGF-1 inhibit the hepatic synthesis of sex hormone-binding globulin (SHBG), thereby increasing the bioavailability of circulating androgens to tissues. Cross-sectional studies have demonstrated inverse relationships between serum SHBG and both insulin and IGF-1. Additionally, sebum production is also stimulated by insulin and IGF-1 [Figure 2].

Inflammation

An important dietary factor that influences inflammation is the relative intake of ω-6 and ω-3 polyunsaturated fatty acids (PUFAs) in food.[24,28] A typical western diet has a significantly higher concentration of ω-6 PUFAs at the expense of ω-3 PUFAs because of the predominance of ω-6 PUFAs in most vegetable oils and processed foods made with these oils. In the current US diet, the ratio of ω-6/ω-3 PUFA has risen to 10:1, whereas in non-westernized diets it has been estimated to be between 2 and 3:1. Hence, the average western diet promotes a proinflammatory cytokine and eicosanoid profile that underlies the development of a variety of inflammatory disorders, including acne. For the acne patient, increased consumption of dietary ω-3 PUFA may be therapeutic because of its ability to suppress inflammatory cytokine production. Also, dietary ω-3 fatty acids are known to inhibit synthesis of the proinflammatory eicosanoids prostaglandin E2 and leukotriene B4 [Table 1]. This hypothesis is certainly reasonable given recent evidence showing that an LTB_4 blocker led to a 70% reduction in inflammatory acne lesions after 3 months.[28]

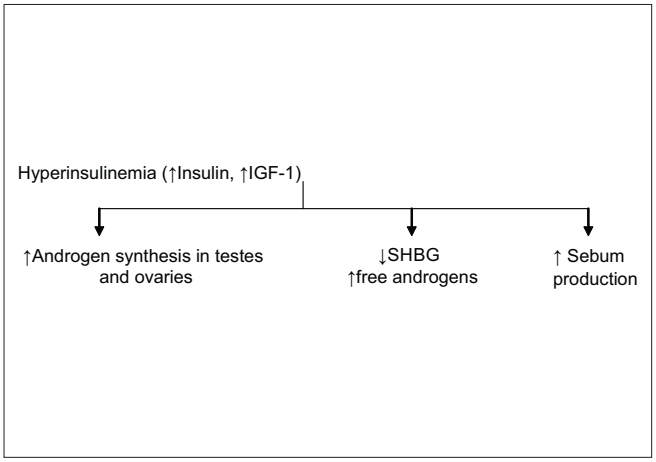

Figure 2: Role of hyperinsulinemia in androgen level determination and sebum production

It has been 38 years since the last diet–acne trial and well-controlled trials are needed to establish the veracity of the diet–acne hypothesis. Future studies will need to test a western diet for acnegenicity in native groups as well as acne efficacy of a primitive diet in westerners. The non-westernized diet that purportedly has a beneficial effect in acne is free of processed food, cereal grains, dairy products, refined sugar and refined oil, and almost entirely comprises unprocessed fresh fruits, vegetables, lean meats, fish and sea food.

PSORIASIS

While susceptibility to psoriasis is inherited, the disease is influenced by environmental factors such as infections and stress, and possibly diet.

The dietary factors that may play a role in psoriasis are as follows:

Energy intake

The prevalence and severity of psoriasis have been reported to be lower in periods of insecure food supply.[29] Therefore, the disease may also be improved by low-calorie diets [Table 2].

Psoriasis also has a positive correlation with body mass index, i.e. more severely affected patients with psoriasis are more likely to be obese and, hence, weight reduction is recommended in obese psoriatic patients. The pathophysiology of both psoriasis and obesity show many shared cytokines, which lead to a state of systemic inflammation. This state of inflammation, better known as the metabolic syndrome, is characterized by hypertension, dyslipidemia and insulin resistance. The link between psoriasis, obesity and subsequent cardiovascular mortality is responsible for the higher risk of myocardial infarction seen among relatively young, severely affected psoriatic patients.[30]

Table 1: Relationship of dietary PUFA to cytokine and eicosanoid profiles in acne

Typical western diet: ω-6/ω-3 PUFA = 10:1 (vegetable oils and processed foods)
Non-westernized diet: ω-6/ω -3 PUFA = 2:1 or 3:1
↑ω-6 + ↓ω-3 → proinflammatory cytokines and eicosanoid profile
↓ω-6 + ↑ω-3 → inflammatory cytokines and eicosanoids (↓IL-1β, IL-1α , TNF-α , IL-6, IL-8, PGE2, LTB_4)

Table 2: Energy intake and psoriasis		
Fasting periods Low calorie diet Vegetarian diet (IL-4)	↓arachidonic acid intake ↓CD4 cell activation ↑anti-inflammatory cytokines ↓oxidative stress	Improvement in psoriasis

Alcohol

Alcohol stimulates histamine release and may thereby aggravate skin lesions.[31] The intake of alcohol is associated with a concomitant increase in the intake of fatty foods and reduced consumption of fresh vegetables and fruits. Hence, alcohol intake should be restricted in psoriasis.

PUFAs

A number of uncontrolled studies have shown the beneficial effect of fish and fish oil supplementation (rich in ω-3 PUFAs) on psoriasis and psoriatic arthritis. The main constituents of fish oil are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The basis for the anti-inflammatory effect of fish oil supplementation is the replacement of proinflammatory arachidonic acid in membrane phospholipids by anti-inflammatory ω-3 PUFAs (EPA and DHA) [Table 3].[32]

PUFA intake in psoriasis

- Daily intake (170 g) of oily fish[33]
- EPA/DHA 1.8 g/day or fish oil (10 capsules three times a day) supplementation[34]
- Parenteral infusion of EPA and DHA 4.2 g/day – useful in acute guttate psoriasis[35]
- Combined ω-3 and ω-6 fatty acid supplementation (rationale: low concentration of PUFA in membrane phospholipids, increased saturated fatty acids and decreased ω-6 fatty acid in psoriatic arthritis, high doses of linoleic acid suppressing LTB_4 production).[36]

Gluten

The relationship between celiac disease and gluten is a well-known one. There is some conflicting data to indicate that there may be an increased incidence of psoriasis in patients with coeliac disease.[37]

Patients with psoriasis have been found to have an increased incidence of IgG/IgA anti-gliadin antibodies compared with healthy controls[38] and one study has also demonstrated that a GFD for a period of 3 months improved disease severity in psoriatic patients with anti-gliadin antibodies.[39]

The suggested mechanisms for this improvement are two-fold: patients with latent gluten sensitivity may have an increased intestinal permeability induced by gluten intake, which can allow the passage of microbes that in turn act as superantigens and worsen psoriasis. The other postulated mechanism is the similar inflammatory cytokine profile (IL-2, IFN-γ) seen in celiac disease and psoriasis, which may be anti-gliadin antibody induced.

Oxidative stress and antioxidants

The presence of oxidative stress and the resultant increase in free-radical generation may play a role in the inflammatory mechanism of psoriasis. The consumption of fresh fruits and vegetables, such as carrots and tomatoes, may be beneficial in psoriasis because of their high content of carotenoids, flavonoids and vitamin C.[40]

A sufficient status of antioxidants (e.g., vitamin C, vitamin E, β-carotene and selenium) may be helpful to prevent an imbalance of oxidative stress and antioxidant defence in psoriasis.[29]

General nutritional status

Extensive psoriasis is known to result in nutritional deficiencies through the loss of proteins and other nutrients in the scales, resulting in hypoproteinemia and macrocytic anemia.[29] Methotrexate decreases the appetite and is contraindicated in patients with a poor nutritional status.

The administration of cyclosporine along with grape fruit juice increases its oral bioavailability and can

Table 3: Properties of ω-6 PUFAs and ω-3 PUFAs	
ω-6 PUFAs	**ω-3 PUFAs**
Linoleic acid (sunflower seeds) Arachidonic acid (meat, egg yolk) ↓ Inflammatory eicosanoids (PGE2, LTB4) + ↑IL-1, ↑ tissue responsiveness to cytokines	Linolenic acid (linseed, walnut oil) EPA and DHA (oily fish – mackerel, herring, sardine, salmon) ↓ Less inflammatory cytokines (PGE3, LTB5) + ↓IL-1, ↓ tissue responsiveness to cytokines

lead to toxicity. Patients on oral retinoids should be advised to avoid foods rich in vitamin A, such as liver.

PEMPHIGUS

Substances such as thiols, thiocyanates, phenols and tannins can precipitate the pemphigus in a genetically predisposed individual.[41] A near-complete list of foods containing these substances includes:[42,43]

- Vegetables: garlic, onion, mustard, turnip, broccoli, radish, cabbage, cauliflower, potato, leek, shallots, chives, tomatoes, ginger
- Fruits and nuts: mango, raspberry, pistachio, avocado, cherry, cashew, banana, cranberry, guarana, pear, blackberry, walnut, peach
- Masticatories and stimulants: coffee, tea, betel nut leaf, katha, cassava
- Beverages: beer, wine, soft drinks
- Miscellaneous: ice cream, candy, baked foods, spices (red chillies), aspartame, sodium benzoate, tartrazine, coloring agents, nutritional supplements
- Water: high tannin content in Brazil river water may be the reason for endemicity of fogo selvagem. Tannins can be removed by chlorination, which would explain why the incidence of fogo selvagem has decreased with urbanization.

Mechanism of induction of pemphigus

- Thiols: Three thiol-containing compounds in garlic (allylmercaptan, allylmethylsulfide, allysulfide) have been found to induce acantholysis *in vitro*[44]
- Isothiocyanates, present in mustard oil, are of two types [Figure 3] – Immunologically reactive compounds (allyl and benzyl isothiocyanate) and irritant compounds (phenyl isothiocyanate)
- Phenols[41]: Phenolic compounds such as urushiol are found in the Toxicodendron family of plants, which are known to cause allergic contact dermatitis and a similar sequence of events may be involved in the acantholysis of pemphigus. Mango, pistachio and cashew belong to the same family of plants. Other phenolic compounds include aspartame (an artificial sweetener), food additives (preservatives, coloring and flavoring agents) and cinnamic acid (present in cinnamon and apple, grape, orange, pineapple and tomato juices).
- Tannins: Tannins are naturally occurring plant polyphenolic compounds with considerable biologic activity. They have been shown to induce acantholysis *in vitro*, which can be blocked by anti IL-1α and anti TNF-α antibodies.[45]

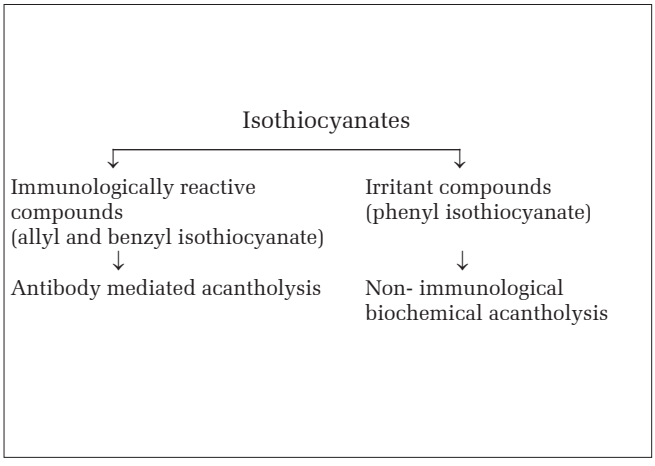

Figure 3: Mechanism of acantholysis of isothiocyanates

Foodstuffs containing tannins include a wide variety of vegetables (cassava, eggplant), fruits (mango, cashew apple, guarana, raspberry, cherry, cranberry, blackberry, avocado, banana, apple, peach, grape and pear), nuts (betel nut, kola nut, walnut, cashew, peanut, pistachio), beverages (coffee, tea, cocoa, beer, wine, soft drinks), spices (ginger, ginseng, garlic, red chillies, asofoetida, coriander, cumin, black pepper, ajwain) and food additives.[44]

URTICARIA

Adverse reactions to food are a frequently discussed cause of urticaria. In acute urticaria, 63% of patients suspect food as the eliciting factor.[46] Both allergic and pseudoallergic reactions (PARs) have frequently been discussed as possible eliciting factors in various forms of urticaria. In adults, the rate of type I allergic reactions is below 1%, although in children, the percentage appears to be higher. PARs against non-steroidal anti-inflammatory drugs (NSAIDs) are responsible for approximately 9% of the cases of acute urticaria, and in a subset of patients with chronic urticaria, a diet low in pseudoallergens has been proven to be beneficial.[47] Type I allergic reactions are only rarely responsible for the development of chronic urticaria. The most likely subgroup of chronic urticaria where type I allergy can be suspected are those patients who suffer from intermittent attacks of whealing lasting for a few hours shortly after the ingestion of food. In contrast, in patients with chronic continuous urticaria with daily whealing, type I allergy is very unlikely to be responsible. In this subset of patients, PARs against food and food additives are strong possibilities, apart from infectious or autoimmune etiology.[46] PARs are difficult to study because the mechanisms involved

are not clarified and oral provocation is the only valid method for testing. Activation of mast cells, resulting in histamine release, has been implicated. Skin test responses are negative and specific IgE antibodies play no pathogenetic role. Diagnosis is difficult because pseudoallergy can only be proved with oral provocation tests. Pseudoallergic urticarial reactions have been shown to be elicited by a broad range of agents, including NSAIDs like aspirin and natural or added food ingredients like salicylates, benzoates and tartrazine. Aromatic volatile ingredients in food are novel agents eliciting PARs in chronic urticaria as demonstrated by a recent study, where reactions also frequently occurred in response to natural ingredients in tomatoes, white wine and herbs.[48]

GENERALIZED PRURITUS

The restriction of dietary protein has been found to reduce the symptoms of uremic pruritus, apart from reducing the complications of chronic renal disease, such as albuminuria.[49] Supplementation of dietary PUFA is said to be beneficial in the treatment of cholestatic pruritus.[50]

ALLERGIC CONTACT DERMATITIS

Approximately 30–50% of individuals who are allergic to natural rubber latex show an associated hypersensitivity to some plant-derived foods, especially freshly consumed fruits. This association of latex allergy and allergy to plant-derived foods is called latex–fruit syndrome. An increasing number of plant sources, such as avocado, banana, chestnut, kiwi, peach, tomato, potato and bell pepper and, recently, turnip, zucchini and cassava, have been associated with this syndrome. The prevailing hypothesis is that allergen cross-reactivity is due to IgE antibodies that recognize structurally similar epitopes on different proteins.[51-53] Some forms of eczema will therefore respond to dietary restriction of certain foodstuffs.[54,55]

The oral intake of nickel can induce systemic contact dermatitis in nickel-sensitive individuals.[56] A flare-up of a recurrent vesicular hand eczema is the most common clinical manifestation of systemic nickel contact dermatitis.[56] The oral intake of nickel depends on the composition of the diet and on factors such as how the food had been prepared, whether it was fresh or canned food and/or whether it was contaminated during processing or by kitchen utensils.[57] Food, water and cooking utensils are all sources of nickel in the diet. Certain foods are routinely high in nickel content, such as cocoa and chocolate, soya beans, oatmeal, nuts and almonds, and fresh and dried legumes.[58]

Food items most commonly mentioned by patients as causing aggravation of dermatitis due to balsam of Peru are wine, candy, chocolate, cinnamon, curry, citrus fruit, tomatoes and flavorings. Avoidance of these foodstuffs would constitute a low balsam diet and may alleviate contact dermatitis to balsam of Peru.[59,60]

Nickel, cobalt and chromium allergies frequently coexist and patients sometimes respond to dietary restrictions of all three metals.[61]

FISH ODOR SYNDROME (TRIMETHYLAMINURIA)

Trimethylaminuria or 'fish odor syndrome' is due to excessive excretion into body fluids and breath of trimethylamine (TMA) derived from the enterobacterial metabolism of dietary precursors such as trimethylamine *N*-oxide (TMAO), choline, lecithin and possibly carnitine and other betaines.[62] TMA is normally cleared effectively by hepatic *N*-oxidation and urinary excretion of the odorless TMAO. Persistent trimethylaminuria in otherwise healthy children is caused by autosomal recessively inherited impairment of hepatic TMA oxidation due to deficiency of flavin monooxygenase 3. The disorder is present from birth but becomes apparent as foods containing high amounts of choline or of TMAO from marine (sea or saltwater) fish are introduced into the diet. Patients with trimethylaminuria may generally be managed by use of dietary restriction of foods with a high TMAO or high choline content and use of soaps with a pH value of 5.5–6.5 to remove any traces of free TMA from the skin. Marine (sea or saltwater) fish (including cephalopods and crustaceans) should especially be avoided, particularly deep sea fish, in which the TMAO content is very high. Foods with a relatively high content of choline, including eggs, liver, kidney and other offal, peas, beans, peanuts, soya products and other legumes should also be restricted.[62]

TOXIC OIL SYNDROME

Toxic oil syndrome occurred in epidemic proportions in Spain in May, 1981. Imported rapeseed oil was required by law to be denatured, typically with castor oil, methylene blue or aniline, to ensure that it was unsuitable for human consumption and went to industrial use. Nevertheless, the sale of rapeseed oil

for human consumption was a lucrative business in Spain. As a result, large segments of the population purchased oil mixtures sold as pure olive oil or other vegetable oils that were marketed as pure olive oil. The symptoms of toxicity resemble scleroderma and graft versus host disease and over 20,000 people were ultimately affected, with over 1,200 deaths from all causes having been recorded.[63]

FIXED DRUG ERUPTION

Artificial flavors, colors and preservatives in foods as well as dyes in medications can rarely be culprits in classic fixed drug eruptions.[64,65]

INBORN ERRORS OF METABOLISM

Phenylketonuria and tyrosinemia

The dietary restriction of phenylalanine and tyrosine is mandatory in these two disorders. The amount of natural protein should be restricted to about 2 g/kg/day in infants and reduced to 1 g/kg/day later in childhood. Protein intake is altered according to plasma tyrosine levels. A supplement of tyrosine/phenylalanine-free amino acids is usually given even if the allowance of natural protein provides enough substrate for growth. Total daily protein requirements for children with tyrosinemia are 3 g/kg for those ≤2 years of age, 2.5 g/kg for those between 3 and 5 years of age and 2 g/kg for those ≤10 years of age. Natural protein and amino acid supplements should provide 10–12% of the daily intake. In addition, essential fatty acids, vitamins and minerals may be supplemented.[66]

Homocystinuria

A low methionine diet is mandatory. Forbidden foods include milk and milk products, meat and fish, wheat, maize, rice, pulses, legumes, nuts and dried fruits. Fruits and vegetables may be consumed in moderate amounts. Foods that need not be restricted are sago, arrowroot, corn flour, custard, sugars, fats, tea and coffee.[67]

Galactosemia

Dietary exclusion of galactose and lactose is necessary throughout childhood. A nutritionally adequate galactose/lactose-free milk should be used during infancy. In later childhood, occasional lactose-free milk and calcium and vitamin supplements may suffice.[67]

Refsum's disease

Phytanic acid is almost exclusively of exogenous origin and dietary restriction reduces plasma and tissue levels. Fish, beef, lamb and dairy products should be avoided. The average daily intake of phytanic acid is 50–100 mg/day, which should ideally be reduced to 10–20 mg/day. Phytanic acid is also present in vegetables but is tightly bound (as phytol) to chlorophyll. Ruminants have the capacity to convert phytol to phytanic acid and the meat of these animals is thus a significant source of phytanic acid. Diets that are very low in phytanic acid (<10 mg/day) are extremely unpalatable and patient compliance is poor. As a consequence, dietary regimens have become more liberal and poultry, pork, fruit and vegetables are now freely allowed. The diet should contain enough calories to prevent weight loss and subsequent mobilization of phytanic acid from fat. In spite of strict adherence to a diet, there may be a time lag before serum levels of phytanic acid start to fall, probably secondary to release from adipose stores. The neurological, cardiac and dermatological sequelae can be reversed by reduction of phytanic acid levels, but the visual and hearing impairments are less responsive to treatment.[68]

G_6PD deficiency

Fava beans (*Vicia faba* or faba bean, thick bean, broad bean, field bean) cause hemolytic anemia (favism) in susceptible individuals. The Greek philosopher and mathematician Pythagoras refused to so much as walk on the fields where they were grown. The fava bean, which is grown throughout the world and is a very popular foodstuff in the Middle East and Southern Europe, is probably the most common trigger of hemolysis in patients with G_6PD deficiency. The significance of other legumes, especially peas, in triggering hemolytic anemia is not exactly known. Although most publications on G_6PD deficiency mention only fava beans in favism, patients often report typical symptoms after eating green beans and chick peas as well.[69]

Xanthomas

In addition to specific therapy with lipid-lowering agents, patients need lifestyle modifications, in which foods containing high concentrations of cholesterol, such as fat, eggs, meat and dairy products are to be avoided.[70,71]

Gout

The standard recommendation for patients with gout is the avoidance of foods with a high purine content, such as organ meat (liver, kidney), selected fish and shellfish, meat and yeast extract brewer, baker's yeast, pulses, certain vegetables (spinach, asparagus) and

fermented milk products. Studies have observed an increased risk of gout among those who consumed large quantities of meat, seafood and alcohol. Although limited by confounding variables, low-fat dairy products, ascorbic acid and wine consumption appear to be protective for the development of gout.[72]

Porphyrias

A 3-week high-fibre diet of natural vegetable/fruit products with a daily caloric content of 1676 kJ/day has been evaluated for porphyria cutanea tarda and is found to be beneficial. In addition, patients with porphyria may benefit from dietary supplementation of carotene-containing foods, such as carrots and green leafy vegetables.[73]

ROSACEA

Tea, coffee, hot beverages, tobacco, alcohol and spicy food are known to precipitate episodes of flushing in rosacea.[74,75]

VITILIGO

The widely held belief in India is that foods that are excessively sour should be avoided by vitiligo patients. These foods include citrus fruits, sour yoghurt, sour pickles etc. The simultaneous consumption of milk and fish is also discouraged. Although there are numerous websites that host dietary advice for vitiligo patients, there is no scientific data to support or refute these beliefs.

It has been found, however, that oral supplementation with antioxidants containing alfa-lipoic acid and vitamin B_{12} before and during NB-UVB broadband UVB significantly improves the clinical effectiveness of phototherapy.[76,77]

APHTHOUS ULCERS

Although the cause of oral aphthous ulcers is unknown, there is a well-established association with coeliac disease. Recurrent aphthous ulceration may, in some cases, be due to gluten sensitivity in the absence of coeliac disease. Studies have evaluated the frequency of anti-endomysial antibodies and villous atrophy in jejunal biopsy specimens in patients with recurrent aphthous stomatitis and, although this frequency was not significantly higher than in controls, the authors concluded that every patient with recurrent aphthous stomatitis should be asked about a history of gastrointestinal complaints and screened for markers of coeliac disease because recurrent aphthous stomatitis may, in some cases, (particularly those with anti-endomysial antibodies or intestinal histologic changes) respond to a GFD.[78-80] Another study, however, attributed the efficacy of a GFD in recurrent aphthous stomatitis to a mere placebo effect.[81]

Studies have suggested allergy to various foods, including figs, cheese, walnuts, tomatoes and fruit. Chronic aphthous stomatitis may be due to food allergy or intolerance to gluten, cows' milk protein and azo dyes and preservatives, elimination of which from the diet, in selected cases, may result in lasting remission of the illness.[82]

CUTANEOUS VASCULITIS

There are instances of cutaneous leukocytoclastic vasculitis occurring in response to food additives such as dyes and preservatives, with instances of vasculitis due to tartarazine and ponceau having occurred in single case reports.[83,84] It may be worthwhile to try elimination diets in selected cases of refractory hypersensitivity vasculitis after ruling out infections, autoimmune disorders and neoplasia.[85]

TELOGEN EFFLUVIUM

Although hair loss has been linked to iron deficiency, there is insufficient evidence to recommend giving iron supplementation therapy to patients with hair loss and iron deficiency in the absence of iron deficiency anemia. Treatment of nutritional iron deficiency anemia includes adequate dietary intake and oral iron supplementation. The practice at the Cleveland Clinic Foundation is to screen male and female patients with both cicatricial and non-cicatricial hair loss for iron deficiency.[86] Although this practice is not evidence based *per se*, the authors believe that treatment for hair loss is enhanced when iron deficiency, with or without anemia, is treated. Iron requirements for vegetarians and vegans are approximately 1.8 times higher than for omnivores because of the bioavailability of ingested iron. Lean meats, especially beef, have high iron contents that are highly bioavailable. Non-animal foods that are high in iron include nuts, seeds, legumes, bean products, raisins, dark green leafy vegetables, whole grains and iron-fortified cereals.[86]

Studies in protein–energy malnutrition, starvation and eating disorders show a positive correlation with hair loss. Profuse hair loss has been seen to occur 2–5 months after starting a vigorous weight reduction program. Rigorous caloric restriction with subsequent inadequate energy supply of the hair matrix is thought to be the cause for the precipitation of the telogen effluvium of the crash dieter.[87,88] The patient's minimum intake should be 0.8 g/kg protein and at least 1200 Kcal per day. Deficiencies of zinc and biotin have also been associated with hair loss; however, there is no concrete evidence to prove their role in the same.[89]

NUTRITIONAL DISORDERS

There are a number of nutritional disorders with dermatologic manifestations that are beyond the scope of this review and will not be dealt with in detail. These include kwashiorkar, marasmus, phrynoderma, pellagra, scurvy, acrodermatitis enteropathica, carotenemia (due to excessive consumption of carrots) and lycopenemia (due to excessive consumption of tomatoes).[70, 90]

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Multiple Choice Questions

1. All of the following foods contain gluten, and hence should be avoided in a patient with dermatitis herpetiformis, except-
   a. Wheat
   b. Rye
   c. Corn
   d. Barley

2. The most common manifestation of cutaneous adverse reaction to food is
   a. Acute urticaria
   b. Pruritus
   c. Flare of atopic dermatitis
   d. Contact urticaria

3. Supplementation of probiotics has a supportive role in which dermatologic disorder?
   a. Psoriasis
   b. Atopic dermatitis
   c. Dermatitis herpetiformis
   d. Acne vulgaris

4. The ideal relationship between the proportion of omega-6 and omega-3 fatty acids in the diet of a patient with acne is
   a. omega-6 > omega-3 fatty acids
   b. omega-3 > omega-6 fatty acids
   c. omega-6 = omega-3 fatty acids
   d. no relationship exists between acne and dietary fatty acids

5. All of the following can precipitate pemphigus in a genetically predisposed individual, except
   a. Thiols
   b. Phenols
   c. Tannins
   d. Gliadin

6. Foods which are high in nickel content include all the following except
   a) Citrus fruits
   b. Nuts
   c. Legumes
   d. Chocolate

7. The inherited deficiency of which enzyme is responsible for the fish odour syndrome?
   a. Trimethylamine oxidase
   b. Trimethylamine reductase
   c. Flavin monooxygenase 3
   d. Choline esterase

8. The symptoms of toxic oil syndrome most closely resemble which dermatologic disease?
   a. SLE
   b. Panniculitis
   c. Scleroderma
   d. Dermatomyositis

9. The average daily intake of phytanic acid in Refsum's disease should be reduced to
   a. 100-200 mg/day
   b. 10-20 mg/day
   c. 50-100 mg/day
   d. 1-2 mg/day

10. Dietary gluten has been postulated to be a possible etiologic factor in all the following dermatologic diseases except
    a. Acne vulgaris
    b. Psoriasis
    c. Dermatitis herpetiformis
    d. Recurrent aphthous stomatitis

Answers
1. c, 2. a, 3. b, 4. b, 5. d, 6. a, 7. c, 8. c, 9. b, 10. a