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PRACTICAL ISSUES AND UPDATES

Take a fresh look at diet and atopic dermatitis

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Abstract
The links between atopic dermatitis (AD) and food allergies are complex, with impaired skin barrier function suspected to play a role in both conditions. Additionally, AD may be the first stage towards other atopic or allergic conditions, such as food allergies and asthma. Thus, early intervention in AD has the potential to interrupt this progression. Contrary to common understanding, large trials support the consumption of allergenic food (e.g. peanuts, dairy products and wheat) in infants to reduce the incidence of food allergies. Supplementing diets with fatty acids and other supplements may decrease the risk of AD, but further study is needed to confirm their efficacy.

Rethink links between atopic dermatitis (AD) and food

Approximately 13% of children are diagnosed with atopic dermatitis (AD), which is characterised by itching, eczematous lesions, dryness and lichenification, typically on the cheeks, limbs and neck [1]. AD is a chronic condition and presents as moderate or severe disease in about one-third of cases [1]. The prevalence of AD is increasing [1], which mirrors the increases reported with atopic and allergic conditions such as food allergies (FAs), asthma and allergic rhinitis [2]. In adults, AD has been linked to many comorbidities, including inflammatory conditions such as urticaria [2].

The link between AD and FAs and/or asthma is well established [1, 2], including in patients with adult-onset AD who had FAs during childhood [3]. In one study, the presence of egg and peanut allergies were 6 and 11 times, respectively, more likely to occur in children with AD [4]; increased allergy rates after the use of peanut- and wheat-containing skin products were also reported [5]. Such findings supported a belief that common food allergens should be avoided in children with AD [1], with now-outdated guidelines discouraging solid food before the age of 6 months [1].

Recent trials in infants suggest the link between AD and FAs is complex [6–8]. Dietary restrictions may increase the risk for FAs [5], whereas supplements may be useful in reducing the risk of AD [5, 9]. This article summarises recent evidence on the role of dietary modification in AD, as reviewed by Rustad et al. [5] and Sweeney et al. [1].

AD may be the first step before other allergies

Both genetic and environmental factors, such as an imbalance in the skin's microbiome (especially with high *Staphylococcus aureus* levels), pollutants, heat and humidity all contribute to abnormal skin barrier function in AD, allowing food-based and/or dust-borne allergens to penetrate the skin's surface [1]. Mutations in filaggrin (FGG) genes are the best known genetic contributors to AD, as FGG is an important component of the skin barrier [1]. The importance of this link was demonstrated in a trial where a decrease in AD severity was reported alongside improvements in FGG and skin barrier function [10].

The pattern of AD followed by an allergic immunoglobulin (Ig) E-mediated condition (e.g. FAs, rhinitis or asthma) raises the possibility that they are all manifestations of the same disease, with atopic sensitisation the common factor [1, 11]. While AD per se is not an allergic IgE-mediated symptom [5], it may represent the first sensitising step in such a sequence [1]. Therefore, it may be possible to prevent progression (i.e. "atopic march") towards FAs via early intervention during childhood [1].

All atopic diseases reflect immune dysregulation, but whether this dysregulation causes, or is caused by, skin

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Table 1 Early trials of dietary supplementation in the treatment of atopic dermatitis based on a review by Rustad et al. [5]

Supplement; putative mechanism of action	Trial details	Efficacy
Oolong tea; contains anti-allergenic polyphenols [14]	Open study in refractory AD in 118 adults	63% of pts reported moderate to marked improvement, sustained in 54% at 6 mo [14]
Oral L-histidine; histidine is an element of pro-FGG, a precursor of FGG [10]	Double-blind, PL-controlled study in 24 adults with AD	↓ AD severity by 34% after 4 wks vs PL; efficacy was similar to that of to mid-potency corticosteroids [10]
Hempseed oil; contains fatty acids that may be beneficial in AD, anti-inflammatory [13]	Randomised crossover study vs olive oil, in 20 adults	↓ dryness, itching and TEWL vs olive oil, ↓ topical medication use and plasma fatty acid profiles changed significantly [13]
Probiotics; may improve or prevent microbial imbalance [15]	Systematic review	Possible benefit in ↓ infantile AD development but no ↓ in AD severity [15]
Vitamin D; may improve epidermal barrier via modulated immune response and ↓ cell proliferation [9]		Improved AD symptoms, best results were achieved when combined with vitamin E; ↓ vitamin D intake noted in women with AD [9]
Vitamin E; improves immune response, via antioxidant action [15]		↓ pruritis, lesion coverage and AD symptoms, ↓ immunoglobulin-E levels [15]

AD atopic dermatitis, *FGG* filaggrin, *PL* placebo, *TEWL* trans-epidermal water loss, ↓ decrease(d/ing)

barrier impairment is unimportant as the respective "inside-out" and "outside-in" hypotheses are both credible [1]. Causation may be even more complex, with the latest "outside-inside-outside" theory suggesting a cycle starting with impaired skin, then immune abnormalities, which in turn worsen the damaged skin barrier [1].

The "outside-in" hypothesis may prime the immune system

An initial allergic sensitisation phase with a subsequent effector phase are the hallmarks of IgE-mediated atopic reactions [1]. Sensitisation in both AD and FAs may be initiated via skin impairment (the "outside-in" view) as abnormally high trans-epidermal water loss is predictive of FAs at age 2 [1].

In AD, imperfect skin function can allow allergens through the epidermal barrier, which primes the immune system for an IgE-mediated immune response [1]. This response is typically driven by mast cells and basophils which react to IgE released from primed B-cells. When the person is later exposed to the allergen (e.g. by eating food containing the allergen), the immune response releases a cascade of pro-inflammatory mediators. The subsequent symptoms of an allergic reaction occurs due to vascular permeability, mucous secretion and other systemic effects such as eosinophilic infiltration and smooth muscle contraction [1].

Only diagnose a food allergy when it exists

A true IgE-mediated FA is rare, with one study reporting that only 1.4% of people have a true FA versus 20.4% of people reporting intolerance to foods [5]. While AD does not manifest as a life-threatening illness, a delayed skin reaction that is mediated by T-cells (and sometimes IgE) can rarely occur 24–48 h after eating food. Confusingly for parents, such eczematous flares may not be true hypersensitivity responses [5].

The gold standard for the diagnosis of food allergies is a closely supervised, double-blind, placebo-controlled food challenge [5]. However, as this is often impractical, IgE serum or skin prick testing (SPT) are commonly used, despite their high false-positive rates in patients with AD; their biggest benefits may lie in excluding FAs as a diagnosis [5].

Despite the rarity of people who have true FAs, proper preventative care must be taken once a FA is identified [12]. Sensitised patients may experience the symptoms of a true FA, such as rash, urticaria, itching, sneezing, swelling, wheezing and gastrointestinal upset and, in severe cases, laryngeal oedema and cardiovascular collapse [12].

Dietary supplementation may be preferred over restrictions…

In light of the atopic march concept, AD therapy aims to avoid progression to FAs and/or asthma, in addition to alleviating itch and other symptoms [5]. Diet may have an important role to play, with supplementation preferred over food avoidance (Table 1). The dual-allergen exposure hypothesis recognises that children are exposed to allergens via two routes: through the skin and by eating. Skin exposure alone may lead to allergies but FAs may be avoided via immune tolerance if allergenic compounds are consumed early enough in life, even in children with AD [5].

Table 2 Positive results in early trials investigating fatty acid dietary supplementation in atopic dermatitis based on a European Academy of Allergy and Clinical Immunology position paper [9]

FatAs and examples of dietary sources	Study type	Efficacy in AD
Saturated FatAs		
Lauric, myristic, palmitic and stearic acids, butter	Epidemiological	In children aged 6–7 yrs, only butter consumed at least 3 × weekly ↓ AD risk vs seafood, fish or margarine
***n*-3 PUFAs**		
α-linolenic and eicosapentaenoic acid, DHA	Epidemiological	↑ concentrations of *n*-3 PUFA, DHA and total LC-PUFA in cord blood ↓ risk of AD; ↑ maternal LC-PUFA at 12 wks' gestation ↓ risk of AD in child at age 14 mo
Fish, flax and chia seeds, algae, walnuts	Epidemiological	Infants and children with AD had ↓ *n*-3 PUFA intake and serum levels
	RCTs	0.9–3.7 g of *n*-3 LC-PUFA supplements during pregnancy ↓ AD in children at age 1 or 2 yrs in a trial
	RCTs	650 mg/d fish oil from birth ↓ AD at 6 mo in high-risk infants
	Small RCTs	In adults with moderate or severe AD, supplementation with fish oil and/or DHA ↓ AD severity vs olive oil or oleic acid (a monounsaturated FatA)
***n*-6 PUFAs**		
Linoleic, ɣ-linoleic and arachidonic acid	Epidemiological	↑ maternal *n*-6:*n*-3 LC-PUFA ratio during the third trimester of pregnancy ↓ risk of AD in children aged 6–7 yrs
	Epidemiological	Infants and children with AD had ↑ *n*-6 PUFA intake
	Small RCTs	In adults with moderate or severe AD, supplementation with linoleic acid ↓ AD vs olive oil or oleic acid
Vegetable oils, seeds	RCT	In healthy infants, DHA plus arachidonic acid supplements from birth ↓ AD risk at 3 yrs

AD atopic dermatitis, *DHA* docosahexaenoic acid, *FatA* fatty acid, *LC* long chain, *n-x* omega-*x*, *PUFAs* polyunsaturated FatAs, *RCT(s)* double-blind, randomised controlled trial(s), ↓ decrease(d), ↑ increase(d/ing)

…do not routinely withhold allergens…

Two large trials (LEAP and EAT [6–8]) demonstrated that withholding allergenic foods may create iatrogenic FAs and this concept should be discussed with all parents of children with AD [5]. Both studies support the early introduction of potentially allergenic food to reduce the incidence of FAs, albeit with some care [6–8]. The LEAP study, a randomised controlled trial (RCT) in 640 patients with AD and/or egg allergies, found significantly fewer peanut allergies occurred 5 years post-trial in those who ate peanut-containing foods as infants (aged 4–11 months) [6]. These results were supported by the EAT study, where 1303 healthy, breast-fed infants (aged 3 months) who consumed cow milk yoghurt, peanuts, eggs, sesame, whitefish and wheat introduced over the first 6 weeks of the trial were less likely to develop FAs or coeliac disease than those who did not [7, 8].

Assessing the risk of serious reactions to allergens is important, with severe AD indicating a higher risk [5]. Prior referral to an allergist is recommended in children with significant IgE test abnormalities (≥ 8 mm SPT reactions or IgE levels of 0.35 kU_A/L or more [13]). However, withholding allergenic foods prior to assessment is not recommended. Parents are likely to overestimate the degree of risk, as 87% of high-risk infants were able to safely consume peanut foods in the LEAP study [6].

In terms of symptomatic improvement of AD, there is no evidence that avoiding allergenic foods is helpful, even in people with a true FA [5]. Studies in other inflammatory conditions include strict exclusion diets designed to minimise inflammation in the bowels and elsewhere; however, these are unproven in AD. Avoiding a wide range of foods is difficult and may result in malnutrition unless a dietitian or nutritionist is closely involved [5].

Restricted nutrition may also worsen intestinal barrier dysfunction, which appears to be related to more severe AD [5]. As with the skin, abnormal epithelial permeability and/or the microbiome are implicated in this process [1]. Antibiotics, antacids and processed foods also contribute to poor microbiomes, which is a risk factor for peanut allergy, alongside increased hygiene and birth by caesarean section [1, 5].

… and consider supplements, but data are limited

Rather than avoiding foods, early trials indicate that several dietary additions warrant more study in AD (Table 1) [5]. These compounds generally have few adverse effects, although excessive doses of vitamins should be avoided as

they can be expensive and dangerous in large quantities. Current evidence for these supplements is weak, with confounding factors such as more attention to diet, and dermatological placebo (and nocebo) effects are likely to affect many trials [5].

Supplementation with fatty acids may decrease the risk of AD

Dietary supplementation with fatty acids (FatAs) in patients with AD has also been trialled (Table 2) [9]. FatAs are used throughout the body in the synthesis of complex lipids, with significant roles in inflammatory and immune processes. Several FAs, including α-linolenic and linolenic acids, are essential as they cannot by synthesised by mammals and must be consumed. Impaired metabolism of essential FAs may contribute to skin barrier disruption, including the lipid makeup of the stratum corneum [9].

The levels and ratios of omega-3 and omega-6 FatAs are relevant in atopic conditions (Table 2), which are broadly anti- and pro-inflammatory, respectively [9]. Of note, arachidonic acid and its metabolites have attracted interest due to their key role in inflammation, and are associated with both anti- and pro-inflammatory properties. Short-chain FatAs are also being investigated as they can influence dendritic and T-cell responses [9].

Despite many inconsistent designs and results, promising efficacy data have emerged from double-blind RCTs in AD (Table 2) [9]. However, adverse events that caused patients to discontinue therapy were reported, such as severe itching with some FatAs (e.g. eicosapentaenoic and docosahexaenoic acid) [16]. Further research and more robust trials of dietary supplementation with FatAs in AD are warranted [9].

Take home messages

- AD is a common atopic condition often associated with allergic IgE-mediated conditions such as FAs and asthma; the impaired skin barrier associated with AD is likely involved in allergen sensitisation.
- The dual allergen hypothesis observes that exposure to allergens occurs via the skin and with food, with fewer FAs and better immune balance developing in children who ingest food allergens as infants.
- The unintended consequences of food avoidance, including iatrogenic FAs, should be discussed with all parents of children at high risk of developing AD or other atopic conditions.
- Small trials in dietary supplements, such as oolong tea, vitamins D and E, histidine, hempseed oil, probiotics and fatty acids indicate potential benefits in AD, but further study is needed to confirm their efficacy.

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