

The Role of Elimination Diets in Atopic Dermatitis—A Comprehensive Review

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Abstract

Background/Objectives: Diet is a common concern for individuals with atopic dermatitis (AD) and their families. Studies regarding the effect of dietary interventions on AD exist, but many are limited by small size and poor design. Conflicting results present a challenge to clinicians seeking to counsel patients. The aim of the current review is to examine the published literature and generate helpful conclusions for clinicians faced with dietary questions in AD.

Methods: A PubMed search was performed focusing on dietary interventions for AD in children and adults through July 2016. The search was limited to the English language and included studies that evaluated one or more forms of dietary modification for the treatment of AD. Studies of supplementation, such as with vitamins, minerals, or probiotics, were not included, nor were studies on prevention of the development of AD. A total of 43 articles met the inclusion criteria and were included in the final analysis.

Results: Trials varied in type, duration, and the AD patient populations studied. Overall, there is some level I evidence to support specific exclusion diets in preselected patients but insufficient evidence for strict elimination diets (diets that are typically limited to six to eight foods). Data supporting other interventions are mixed and based on small, poorly designed studies.

Conclusions: A comprehensive literature review reveals some promising results and several areas in need of further study. More evidence is needed to form a strong foundation for recommendations regarding the utility and role of elimination diets in AD management, but current evidence suggests that strict diet management is not effective in the treatment AD in the vast majority of patients.

Atopic dermatitis (AD) is a relapsing inflammatory disease characterized by chronically dry skin, intense pruritus, and eczematous skin lesions. AD is common, usually manifesting in infancy and affecting up to

20% of children worldwide (1). Although most agree that AD is the result of a complex interplay of genetic, environmental, and immunologic factors that probably involve a dysfunctional skin barrier, complete

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understanding of its etiology is elusive (2). Such unsatisfying answers have led physicians and patients (or their families) to implicate diet with causation or worsening of AD symptoms. The recurring, relapsing nature of the disease complicates attempts to discern whether there is a true causal relationship or merely an observer-expectancy effect or other bias. Under-scoring this, studies have shown the marked placebo effect of dietary interventions in other settings (3).

The collective literature has produced mixed results but seems in aggregate to suggest that strict diet management is not effective in the treatment of AD, at least for the vast majority of patients. At the same time, certain case reports and isolated empirical trials suggest that there may be subtleties that warrant closer investigation.

PATHOPHYSIOLOGY

Current knowledge of the pathogenesis of AD supports a link between sensitization to food allergens and AD skin lesions. It is widely accepted that loss-of-function mutations in the *FLG* gene, which encodes the protein filaggrin that aggregates keratin filaments and interacts with lamellar bodies to create a protective barrier in the skin, are central to AD's pathophysiology (2). This impairment of the skin barrier has been shown in murine models to lead to greater penetration of allergens through the skin and enhanced sensitization to allergens (4,5). Eczematous skin lesions host vast numbers of epidermal and dermal dendritic cells (DCs), which express high-affinity receptors for immunoglobulin E (IgE) that enable cells to take up a wide range of allergens and have been found in greater numbers with greater skin lesion severity (2). It is thought that such mutations may predispose individuals with AD to epicutaneous sensitization to food and environmental allergens, a phenomenon that may in part explain the correlation between AD, food allergy, allergic rhinitis, and asthma that defines the "atopic march." This mechanism may explain the subsequent development of food allergies in individuals with AD and exacerbation of AD with food allergen ingestion. Conversely, it implies that this sensitization is an epiphenomenon of AD and that food exclusion would thus not necessarily influence the natural course of the disease (6).

TESTING

Appropriate testing for food reactions is important but challenging. It is estimated that 80% of children

do not experience worsening of their AD due to food allergy (7), although patients perceive adverse reactions to food at a rate 10 times as high as their true prevalence (8). Evaluating for AD aggravated by food allergens ideally involves restricting suspected foods, allowing the dermatitis to clear over the course of 3 to 7 days, and then performing an oral challenge (7). Oral challenges are time intensive and put the patient at risk of severe reactions, but they are the only conclusive test for food allergies—especially when differentiating eczematous reactions or exacerbations from simple urticarial reactions (9). At present, double-blind placebo-controlled food challenges (DBPCFCs) are considered the criterion standard for diagnosing food allergies to minimize the role of subjective influences on the observed outcome (10).

Given the inherent difficulty of routinely performing DBPCFCs, multiple serum and skin tests are used to diagnose food allergies in the setting of AD. We briefly review some of the common tests used for diagnosis of food allergies.

AD is often associated with specific antibodies to allergens and with high serum IgE levels (11). Some studies have suggested that the latter is correlated with the severity and duration of AD (12). Nevertheless, although total serum IgE can increase after allergy provocation, this elevation is not necessarily related to current allergic disease activity (12). Additionally, normal IgE levels can be seen in individuals with AD (12), making this an imperfect correlate for food allergies or AD severity.

Serum-specific IgE (sIgE) is commonly used to screen for food allergy in individuals with AD (9), but a recent large-scale study concluded that sIgE should not be used in place of oral food challenges for food allergy diagnosis and tailoring of food-elimination diets given its high false-positive rate (9). The authors found that, in general, low sIgE levels have a high negative predictive value for food allergy, whereas high sIgE levels have a low positive predictive value—limiting this test's usefulness for confirming or refuting a diagnosis in patients who already have strong historical indicators of allergy (9).

sIgE is often used in conjunction with skin prick tests (SPTs). Together, sIgE and SPTs can confirm sensitization to an allergen, but neither alone can reliably ascertain a food allergy (12). In the case of SPTs, allergen exposure leading to urticaria, rash, or pruritus confirms skin reactivity to an allergen, but such reactions do not always correlate with systemic inflammatory reactions after exposure of allergens to the gastrointestinal tract, which further complicates the matter (12).

Several other serum studies are commonly used to assess food allergy and the effect of diet on AD. IgA and IgG have frequently been used as surrogate markers of food allergy, but evidence suggests that IgG and IgA levels do not correlate well with clinical parameters of AD (13). A 2003 review of diagnostic approaches to food allergy found that it is normal to produce specific IgG, IgG4, and IgA in reaction to many common foods in the absence of manifesting food allergy and concludes that there is no evidence to support the validity of using specific IgG to diagnose food allergies or intolerances (14). In another study, levels of specific IgG did not significantly differ between individuals allergic to milk and a control group (15). Lastly, a 2005 review observed that multiple studies have similarly failed to demonstrate the utility of specific IgG or IgG4 testing for the diagnosis of food allergy (16).

Given some reports of an association with AD disease activity (12), blood eosinophil levels are also commonly reported. Similarly, some studies report measures meant to extrapolate eosinophil activity, such as eosinophil cationic protein (ECP), although the data suggest that ECP can be high in individuals with AD and individuals without eosinophilia (12).

The complex landscape of testing further complicates the identification of food allergens and the evaluation of elimination diets.

METHODS

A PubMed search was conducted to identify all studies reporting dietary therapies for AD. Medical Subject Headings (MeSH) used in the literature search included “eczema” or “atopic dermatitis” or “atopic eczema” and “dermatitis, atopic/diet therapy.” The search was conducted through July 2016; no other date restrictions were used.

Publications were limited to those in English and studies of one or more human subjects, including adults, adolescents, children, or infants with AD. We excluded trials that did not examine AD as the primary disease process and those that did not evaluate a form of diet elimination therapy as a primary intervention. Studies that investigated alternative forms of dietary manipulation (e.g., dietary additions) or dietary supplementation or examined maternal diet were also excluded. The primary outcomes of interest were clinical signs and symptoms, long-term control of AD, and quality of life. Case studies meeting the above criteria were included.

We conducted a manual review of the titles and abstracts identified from the literature search.

Additional articles were identified by review of the reference lists in the key articles. We obtained the full-text articles and determined eligibility again after review of the entire text. We were not blinded to the names of journals, authors, or institutions. The patient population, study design, dietary intervention, and outcome measure were recorded for each study. Conclusions are based on the evidence provided within each study.

RESULTS

The initial search using MeSH as outlined above yielded 136 articles, of which 37 met inclusion criteria and were selected for review. After identification of additional manuscripts through reference lists in the key articles and after full-text review, 43 were included in the final analysis. One paper (17) presented data found in two other papers (18,19) and was therefore excluded from our analysis.

Efficacy of Specific Exclusion Diets in Unscreened Patients

Perhaps more than any other food items, cow's milk and eggs are anecdotally considered to be two of the foods most often responsible for childhood allergies and, as such, they are disproportionately targeted for elimination diets, even in populations with no history of food allergy to either.

Several studies have shown a benefit to an egg and cow's milk exclusion diet in children with AD. One study placed two demographically similar groups of children with AD (78 and 84 patients) on an egg- and cow's milk-free diet (followed by a general elimination diet for those who did not respond to the initial diet) and found that 53% of children in the first group and 27% in the second group had more than 50% improvement in clinical severity scores with either diet strategy (20). Although patients were not recruited based on prior allergy testing results, at least one food intolerance was found in postintervention open oral provocation tests in all patients who improved—most of which were milk or egg—suggesting that improvement in these patients may have been due to elimination of a true food allergy; this study was limited by significant dropout rates in both groups and the lack of placebo control and blinding, which may have influenced not only the initial results, but also the subsequent oral provocation tests via confirmation bias.

Another study placed 59 children on a 4-week elimination diet of cow's milk, eggs, or both

(depending on what was present in the diet at the time of AD onset), after which 80% saw clinical improvement (21). The mean age of responders was significantly younger than the nonresponding group (3.5 vs 4.7 yrs) ($p < 0.01$), leading the authors to suggest that allergy to milk and eggs was almost certainly responsible for the improvement in younger children, whereas the lack of improvement in nonresponders may have been due to the presence of other offending foods in the more diverse diets of older children. At the same time, there was no difference in initial AD severity or IgE titers between the two groups. The authors concluded that allergies to eggs and cow's milk play an important role in eczema and that SPTs and IgE tests are not helpful for predicting who will benefit. Despite the high response rate and encouraging findings, the lack of data regarding the number of patients who were placed on each diet and of placebo-control and blinding limit this study.

A well-designed crossover study of 36 patients evaluated the effect of an egg and cow's milk elimination diet on eczema activity, disease area, pruritus, sleep disturbance, and antihistamine use (22). This double-blind randomized controlled trial (RCT) randomized patients to a 4-week diet starting with a soymilk substitute or a placebo containing milk and egg. Patients underwent a 4-week washout period with a normal diet, followed by a 4-week trial of the other intervention (soymilk substitute or placebo). Although only 20 patients completed the study, 14 responded favorably to the trial diet, with significant improvement in four of the five areas evaluated (activity score, area score, sleep disturbance, antihistamine use). The authors concluded that diet treatment can play a role in AD treatment. The study also concluded that SPTs do not provide information of therapeutic relevance—all patients had a positive SPT, and there was no correlation between SPT results and response to the trial diet. The strengths of this study include a strong design and the fact that multiple domains of AD were evaluated, although the small sample size, low completion rate, and inability to draw conclusions about patients' food allergy status limited the study.

Other studies of specific exclusion diets in unselected patients have shown little or no benefit, suggesting that exclusion of milk or eggs in patients without food allergies has no role in the treatment of AD. In a double-blind RCT with a crossover phase, 40 patients completed a 6-week egg and cow's milk exclusion diet with soy substitute (23). There were no statistically significant differences in skin area affected, itching, or topical steroid use between

the treatment diet and normal diet or control diet. The low response rate (25% improved on trial diet) led the authors to conclude that there is only a minimal benefit to exclusion diets in unselected children. Furthermore, improvement was not correlated to an SPT, IgE, or radioallergosorbent test (RAST). Another study found that a milk exclusion diet resulted in clinical improvement in half of the infants placed on the diet, but the trial's methods and results were too poorly reported to reach any definitive conclusions (24). Lastly, a case report noted clinical improvement in two children after a milk elimination diet, but these results do not account for the possibility of spontaneous remission or elimination of a true food allergy, given that no allergy testing was performed (25).

The mixed results of these studies make it difficult to draw a conclusion regarding egg and cow's milk elimination diets in children with AD who are not preselected. Even the level I evidence is mixed, with one trial (22) showing significant improvement and two smaller trials (23) showing no benefit. Although studies with stronger designs have failed to make a compelling case for egg and cow's milk elimination diets, the wealth of positive results from other trials and case reports remain encouraging and may inspire others to pursue further study in this area with larger, more robust trials.

Efficacy of Specific Exclusion Diets in Preselected Patients

Instead of broadly applying cow's milk or egg exclusion diets to all individuals with AD, a number of studies have explored the application of these diets in patients with some evidence of allergy to the specific allergen in question. These studies vary in their methods for determining food allergy, employing a range of tests to establish inclusion criteria, such as SPTs, serum IgE testing, and oral provocation tests.

Multiple studies have used a combination of RAST and SPT to identify food allergens and develop food elimination diets. An egg elimination diet was prescribed for 213 patients younger than 3 years old and their breastfeeding mothers in egg-allergic and non-allergic children (as determined by a positive RAST or SPT) (26). All patients were placed on the elimination diet regardless of allergy status and AD was assessed as better or worse after 2 weeks. Analysis according to age group showed that AD improved for more than 48% of all 3- to 6-month-old children and 44% of those 7 to 11 months old, whereas improvement was rare in other age groups. Clinical improvement was

significantly associated with egg allergy in the 3- to 6-month-old cohort only—a cohort that was breast-feeding. Strengths of the study include its large sample size, blinded design, and presence of a control group, comprising children without allergy to egg (as determined by RAST or SPT). Study weaknesses include a binary assessment tool and high dropout rate (35%). The lack of significant results in other age groups in this well-designed study tempers enthusiasm for the use of RAST or SPTs as the foundation for shaping elimination diets.

In a single-blind RCT, 62 patients with high specific IgE to eggs were randomized to 4 weeks of an egg exclusion diet and AD management advice or AD management advice alone (27). The mean reduction in surface area affected and in severity score was significantly different between the treatment ($p = 0.02$) and control ($p = 0.04$) groups. Although the magnitude of change was small (28), this study suggests that children with AD and egg sensitivity may benefit from an egg-free diet. The authors also suggest the need for further studies with longer dietary modification, given the slow change in skin findings.

Multiple studies have incorporated oral food challenges, open food challenges, or DBPCFCs to help identify foods for elimination. Eleven patients who were considered to have an egg allergy (based on having at least one positive SPT, atopy patch test, or sIgE test result to egg and a positive open provocation test to egg or positive history of adverse reaction to eating egg) underwent an egg elimination diet (29). The elimination diet resulted in improvement in 6 of the 11 patients, leading the authors to conclude that egg allergy may exacerbate eczema in certain patients. In addition to the small study size and lack of placebo and blinding, the use of highly unreliable testing methods to identify individuals with egg allergy limited this trial.

Two studies used DBPCFC alone to identify food allergies. A 9-month study of 45 children with AD with cow's milk allergy (proven by DBPCFC) tested the efficacy of an amino acid or extensively hydrolyzed whey formula (30). Although one of the primary outcomes of the trial was the safety and nutritional adequacy of the formulas, the trial also assessed AD severity and noted a significant reduction in SCORing of Atopic Dermatitis (SCORAD) measurements for both groups ($p < 0.001$), with a mean SCORAD score of 4 for amino acid and 5 for whey formula after 8 months. The mean starting SCORAD scores of 21 for the amino acid group and 17 for the hydrolyzed whey formula group reflect overall mild disease (28). In

another study of 73 infants with cow's milk allergy (also proven by DBPCFC), patients were randomized to receive an amino acid-based formula or extensively hydrolyzed whey formula (31). Significant improvement in SCORAD was observed in all patients after 6 months. Together, the findings from these two trials suggest that dietary elimination of cow's milk in patients with a positive DBPCFC improves AD, but because there was no control group in either trial, spontaneous disease remission or a placebo effect cannot be excluded as the underlying cause of these encouraging results.

Finally, one particularly unique Japanese multicenter trial examined the efficacy of replacing dietary rice and wheat with hypoallergenic rice (HRS-1) in 44 patients with refractory AD and suspected rice allergy as ascertained by a history of a positive elimination test, positive oral provocation test, or positive RAST (32). HRS-1 replacement of rice and wheat not only resulted in a statistically significant improvement in the AD Affected Area and Severity Index (ADASI) score, but the authors also observed a “moderate-remarkable” reduction in topical corticosteroid use despite the fact that the participants all had recalcitrant AD that was resistant to past steroid use. Although the lack of controls and blinding limited these encouraging results, they suggest that rice and wheat elimination diets may be of substantial aid for individuals with refractory AD with suspected rice allergy.

The overall findings from trials involving preselected patients are mixed, and limitations in the size and design of most studies reviewed here at least partially obscure any potential benefit from elimination diets in this population. Nevertheless, studies that used RAST or SPT to determine food allergies (26,27,29) had mixed conclusions and less enthusiastic findings than those that used DBPCFC (30,31). The level I evidence in this cohort (27,31) indicated significant AD improvement when exclusion diets were used in groups with identified food allergies. The results of these studies are encouraging and suggest that specific exclusion diets based on verified food allergies (preferably via DBPCFC) are a worthwhile avenue for further research in AD management.

Efficacy of General Elimination Diets

One question in the realm of diet therapies is whether identification and elimination of unsuspected food triggers can improve chronic AD (33). Therefore it is only through dietary manipulation and elimination

that provoking foods can be identified. A general elimination diet—in which all food items are eliminated from the diet except for a predetermined set of 12 to 20 foods generally suspected to be hypoallergenic (e.g., lamb, chicken, rice, carrots, potato, corn, salt, water, oils)—is one of the most common treatment modalities observed in the diet therapy literature, probably because of the relative ease of implementing a trial without tailoring the intervention to each participant.

In a study of 15 children, a general elimination diet reduced the AD severity score by at least 70% in 60% of patients (34). All patients with high total IgE, at least one positive RAST, and at least one positive SPT responded to diet therapy, suggesting that elimination diets may be helpful for those with food hypersensitivities.

A study of 29 children with AD on a 2-week elimination diet showed statistically significant improvement in mean itch score and total area affected by eczema but not in sleep disturbance or clinical severity scores (33). Only 13 of the 29 children completed the trial and only 5 of the 13 showed improvement in clinical severity scores. Only 2 of the 12 children who completed the diet and underwent reintroduction challenges were able to identify foods that provoked eczema symptoms. More troublingly, the authors observed parallel clinical score improvement in three of eight children who stopped the elimination diet during the same time period, which may indicate other reasons for improvement. Similarly, another small study of 13 patients observed some degree of improvement in all 8 who completed the elimination diet, but 4 returned to a normal diet without deterioration, again highlighting the inability to exclude spontaneous remission (35).

Lastly, a poorly reported study placed 130 children on an unspecified elimination diet and found that 38% of the subgroup of 50 children younger than 3 years experienced remission of symptoms, whereas no remissions were seen in any subgroup of older children (36). The results of this study are of dubious value; in addition to lacking controls and blinding, this study failed to specify what type of elimination diet was used or to report how symptom improvement was assessed.

It is challenging to draw concrete conclusions from this cohort of studies, given the overall small size and limitations of study design. From the limited evidence, it seems that a general elimination diet may be of benefit to a subset of individuals with AD, but none of the evidence provided was of level I quality, and larger trials with more rigorous study designs are needed to

assess the value of an elimination diet for AD and exclude the contribution of spontaneous remission or placebo.

Efficacy of Tailored Elimination Diets

The concept of a tailored elimination diet makes intuitive sense; based on previous positive allergy or intolerance tests, the offending agents are selectively removed from the diet. Identifying and eliminating only incriminating foods allows patients greater dietary freedom than with general elimination diets.

Multiple studies have shaped elimination diets based on oral challenges varying in design from open (nonblinded) to DBPCFCs. A 3-year prospective study of 100 children with AD had positive results with an elimination diet based on positive DBPCFCs (37). The authors found that the tailored elimination diet not only significantly improved mean SCORAD scores but also reduced mean topical corticosteroid use and total serum IgE levels. The results of this study are some of the most encouraging, because they lend powerful evidence to the idea that elimination diets can be of help in those with true allergy, as confirmed by DBPCFCs. Similarly, another study placed 44 children with AD with food intolerances on a tailored elimination diet. Diagnosis of food intolerance was based on open, oral provocation tests and RAST (when possible) (38). The elimination diets resulted in moderate to marked improvement in 40 of 44 patients. Although a lack of placebo control and blinding and the fact that food intolerances and allergies were determined using oral provocation tests rather than DBPCFCs limited this trial, the overwhelming response rate to diet therapy in those found to have food intolerances is heartening.

Many studies use SPT alone or in combination with other tests to identify food allergies for exclusion. A tailored elimination diet based on history and SPT results resulted in statistically significant improvement in clinical skin scores in 49 of 66 patients who completed the trial (39). Furthermore, 64 of 66 patients who responded to the elimination diet underwent a subsequent series of DBPCFCs to commonly allergenic foods and were found to be significantly more likely to react adversely to at least one food item than nonresponders. (The food challenges were not correlated with initial history or SPT results.) Like many of the trials, a lack of controls and blinding and the significant number of originally recruited patients (25 of 91) from whom adequate data could not be collected limited this study. In a larger study, 154 children with AD underwent a

1-year individualized elimination diet based on patch and prick testing (40). The elimination diet significantly reduced the number of allergic rashes, significantly decreased medication use, and significantly improved the clinical course as evaluated by SCORAD and patient subjective assessments, but in addition to the usual limitations, this study was limited by the large proportion (29%) of participants lost to follow-up.

Finally, a controlled study examined the efficacy of an elimination diet alone, individually tailored to exclude foods based on the results of Multiple Allergen Simultaneous Test/fluoro-allergosorbent testing and SPT testing (41). The tailored elimination diet resulted in statistically significantly greater improvement in clinical severity score than in the control arm and significantly lower eosinophil counts, although IgE levels were not significantly different between groups. On postintervention DBPCFCs, only 77.8% of patients had an adverse reaction to at least one food, leading the authors to call into question the accuracy of serum IgE and SPT in determining true allergies. In the second part of the study, the authors compared the efficacy of tailored elimination diet alone with that of interferon gamma (IFN- γ) therapy alone and that of both interventions together and found that the combined interventions led to a greater improvement in symptom score than either therapy alone. Although not statistically significant, these results led the authors to conclude that concomitant diet therapy is necessary for successful IFN- γ therapy—or conversely, that supplementation of IFN- γ therapy may be of additional benefit for those undergoing diet therapy. In either case, further trials are needed to elucidate whether this synergistic effect is real.

The strikingly positive results of these larger studies, in addition to the similarly encouraging results from other smaller studies and case reports (42–44), lend credence to the use of tailored elimination diets as treatment for AD, although given the current lack of level I evidence, larger, more robust studies are needed to establish the validity of these preliminary findings. At the same time, it is equally important to elucidate the best, most efficient methodology for identifying food allergies if such diets are to find any success.

Efficacy of Strict Elimination Diets

Strict diets such as the Six Food diet, Few Foods diet, or elemental diets are elimination diets taken to a further extreme; patients are placed on a diet

consisting of the fewest number of hypoallergenic foods possible to exclude any other potential food-related source of symptom exacerbation. The Six Food diet, as the name suggests, permits only six foods for consumption, and the Few Foods diet may consist of anywhere from 1 to 19 foods (with most ultimately including 5 to 9) in the trials reviewed here. In both of these diets, permitted foods are selected from a list of foods suspected to be hypoallergenic (as in general elimination diets). Elemental diets lie on the furthest end of this spectrum, consisting only of the most basic components of foods: amino acids, glucose, vitamins, minerals, and oils.

Multiple studies have explored the efficacy of an elemental diet. A study of eight children with severe, refractory AD on an elemental diet (Vivonex formula, Nestle Health Science, Vevey, Vaud, Switzerland) for 6 weeks to 1 year found that the diet significantly reduced clinical severity scores (45). All patients underwent postintervention RASTs and SPTs, and all had at least four positive RAST scores, suggesting the presence of multiple food allergies that may have contributed to AD exacerbations. Limitations of this study include the small study population, lack of placebo control, and lack of blinding. Another study of 40 patients combined the elemental diet (Vivonex) with hospitalization and exposure reduction to home pet and dust mites (18). The high rate of sustained disease improvement (73%) led the authors to conclude that antigens can be beneficial for some individuals with severe AD, although the need for intensive monitoring and risk of side effects makes the intervention an option of last resort. Although the lack of control group limited the study, the authors maintained that the sustained response seen after hospital discharge indicated that it was unlikely that the response was related to avoidance of environmental allergens alone. One of the previously mentioned studies also included an elemental diet intervention (24). Improvement in clinical severity scores was seen in 80% of those on the elemental diet (130 patients), but adherence was not discussed. Failure to define clinical improvement and a lack of statistical analysis make it difficult to interpret this study properly.

Another study took this strategy to its logical extreme by placing nine children with refractory AD on total parenteral nutrition (a dextrose and electrolyte solution) for 8 to 17 days (46). Although all patients had failed to improve on a previous elimination diet, the clinical severity scores of seven of eight who completed the trial diet greatly improved. Although it is encouraging to consider total parenteral nutrition as a viable last-resort alternative for

refractory AD, the small study population and lack of controls and blinding, which are particularly important given the potentially confounding effect that the hospital environment confers, significantly limited this study.

Two other studies also showed tentatively positive results. One placed 21 infants and children on a strict elimination diet and observed improvement in almost all (47). The other found improvement in all 16 children with suspected multifood-induced AD placed on a strict meat-based oligoantigenic diet (the Rezza–Cardi diet) (48). The small size and lack of controls similarly limited these studies.

In contrast, several studies have shown a lack of short-term or long-term benefit of strict elimination diets. One study placed 63 children with AD on a six-food diet for 6 weeks and observed significant clinical improvement in 52% (19), but 43 patients were followed for 12 months, at which point the median disease severity score was the same regardless of initial response and the final outcomes were similar because of the tendency of all patients' AD to improve over time. The absence of a control group makes it impossible to differentiate response due to the placebo effect from that due to antigen avoidance.

A study of 66 patients introduced a tailored Few Foods diet (mean 8.76 foods) based on history, SPT, and sIgE results and found improvement in the visual eczema score in only 15 patients (49). Ten of the 15 diet-responsive patients subsequently underwent DBPCFC, but there was no significant difference in the visual eczema scores between the active and placebo periods—again suggesting the inaccuracy of SPT and sIgE in allergy identification. Given these potentially conflating factors, the failure of the results to reach statistical significance in an uncontrolled, nonblinded trial, and the failure to observe any difference during the DBPCFCs, the authors concluded that elimination diets confer only limited—if any—benefit.

Finally, results of a double-blind RCT evaluating 33 adults on an elemental diet (Vivasorb) or placebo (blended hospital diet) showed no difference in disease activity or laboratory studies between groups, suggesting that food intolerance plays little role in the pathogenesis of AD in adults (50). Another RCT placed 85 patients on a Few Foods diet or a normal diet and observed improvement in all groups, inadvertently highlighting AD's relapsing–remitting nature instead of any potential benefit from the diet (51).

Although the evidence regarding the possible benefit of strict elimination diets appears mixed, larger trials with stronger study designs have failed

to show a benefit. Small sample size and poor study design, including a lack of control groups, limited all five studies showing possible benefit. Conversely, neither trial with level I evidence (50,51) found a difference between treatment groups. Furthermore, the fact that another study failed to find a difference in AD severity at 12 months regardless of response to the trial diet is important because it highlights the need for long-term follow-up to truly evaluate the effect of diet. As a group, these studies illustrate the controversy surrounding the benefit of strict elimination diets.

Efficacy of Caloric Restriction

Caloric restriction for the treatment of AD is based on the idea that undernutrition (without malnutrition) can have a beneficial effect on inflammatory disorders (52). In mice models, short-term fasting was shown to improve allergic contact dermatitis (53), and long-term dietary restriction suppressed dermatitis progression in a mice model for AD (54). Although the mechanism is unclear, two studies have been conducted based on this principle.

One study evaluated this strategy by hospitalizing 19 patients with AD for 8 weeks and giving them a carefully managed low-energy diet (52). The low-energy diet significantly improved mean SCORAD scores. A decrease in body mass index (BMI) was also significantly associated with a decrease in symptom intensity scores, and in the severe AD subgroup (SCORAD >40), 8-hydroxydeoxyguanosine levels in urine (a marker of oxidative DNA damage) were shown to decrease significantly. Although this study provides an interesting perspective on a different form of diet therapy, it is difficult to characterize how much of the clinical improvement was simply due to the hospital environment or the placebo effect in the absence of proper controls. A decrease in oxidative markers after a decrease in BMI is consistent with literature showing obesity to be a proinflammatory state (55) and the association between obesity and greater prevalence of AD (56). A similar study hospitalized 20 patients and placed them on a combined low-energy vegetarian diet and observed significant clinical improvement, although most of the patients were found to have multiple positive RASTs, suggesting another possible mechanism for how the limited diet and hospital environment may have contributed to improvement (57). Finally, based on the same principles, a case was reported in which weekly short-term fasting for 20 weeks improved SCORAD scores for a 23-year-old woman (58).

(Twenty-four-hour fasting was conducted once a week for a period of 20 weeks. On the fasting day, the amount of energy intake was 200 kcal.)

Any intervention regarding caloric restriction merits intense oversight. Although the results of these studies appear encouraging, their designs hinder the ability to draw conclusions regarding the effect of caloric restriction on AD. There is no level I evidence within this group of studies, highlighting that better-designed studies are needed. Regardless, the severity of this intervention would limit it to an intervention of last resort.

Efficacy of Other Dietary Interventions

The effect of other unique dietary interventions has been reported in several studies. The relationship between metal sensitivity and the etiology and aggravation of AD is unclear (59). One study examined the effectiveness of a low-metal diet and concurrent removal of metal dentures when applicable for 27 patients, all of whom had a positive patch test to at least one metal antigen (59). In 67% of patients there was moderate to marked clinical improvement and a statistically significant decrease in blood eosinophil and lactate dehydrogenase levels 3 months after the intervention. In the 33% of patients who showed minimal or no improvement, there was no significant change in blood eosinophil or lactate dehydrogenase levels; the authors suggested that some patients may have had false-positive patch test reactions given the difficulty in distinguishing irritant patch reactions from true reactions. Although the uncontrolled nature of the study limited these results, they suggest that low-metal diets may confer clinical benefit for patients with true metal allergies.

A second randomized, single-blind, placebo-controlled study of 21 patients investigated a low nickel diet combined with oral disulfiram (a nickel-chelating agent) supplementation in 21 patients with chronic dyshidrotic hand eczema and positive patch tests to nickel and found that the combined intervention improved the AD severity score significantly more than placebo (normal diet and placebo pills) (60). Although the results of this trial were striking—10 of 11 patients in the experimental arm had complete clearance of their eczema, compared with 1 of 10 in the control group—the relative contributions of the low-nickel diet versus the oral disulfiram supplementation cannot be determined without further trials. In addition, this study included only patients with dyshidrotic eczema, as those with atopic diathesis were excluded from the study.

There is also little research regarding the relationship between AD and food additives, although reports of AD in response to ingestion of artificial coloring and balsam of Peru (which contains multiple food flavoring substances) have been documented (61). Based on these reports, the role of natural or artificial flavoring elimination with supplemental ketotifen and disodium cromoglycate was analyzed in 11 children with AD and positive DBPCFC (or positive SPT and positive RAST) to balsam of Peru, vanillin, or vanilla. At 3 months, the elimination diet resulted in subjective improvement in 5 of 11 patients and cleared AD completely in 2 others. At 9 months, four relapses were observed; in two of these cases the diet had been abandoned. Overall, these highly suggestive results (improvement in 64% of participants) pose yet another interesting angle from which to approach diet elimination in AD, although the small study population, lack of placebo and blinding, and lack of an objective measure of clinical improvement make it difficult to seriously consider this strategy without further trials.

Based on the popularity of a sugar-free diet in German patients, a study investigated the role of sugar in AD by placing 30 subjects on a sugar elimination diet for 1 week followed by a DBPCFC to sugar with sucrose as placebo (8). There was no significant difference in SCORAD scores or ECP levels after the elimination diet or after the DBPCFC. These results suggest that dietary sugar is not an aggravating factor in AD.

Lastly, one case report of a 4-year-old girl reported complete remission of AD symptoms after switching to low-sodium, low-calcium table water (62). Symptom remission was attributed to the water change rather than to spontaneous remission given that the positive response was elicited twice and relapse was observed in between. The results are plausible given that AD has been observed to fluctuate in response to calcium and sodium in the diet (63,64). More trials are needed to determine the validity of this approach.

Based on the evidence provided, low-metal diets in those with metal allergies may be an area worthy of future investigation. Although small size and overall study design limited the results, they appear promising. Overall, the weak study designs and the singular studies for the other dietary interventions described above make it difficult to identify areas of future promise.

DISCUSSION

The cost of AD is remarkable, with direct and indirect costs totaling more than \$4.23 billion in 2004 (65).

Equally important is AD's effect on quality of life, including the effects of itch and pain and their subsequent repercussions on a patient's time, social life, occupation, and self-esteem (66). Without a clear etiopathogenesis or cure, patients continue to seek relief from this disease and dietary modifications continue to be of tremendous interest. Although scientific attention to researching dietary interventions appears to have paralleled that of the general population, the majority of investigations have failed to reach the level of significance necessary to make broad conclusions about their efficacy.

Large-scale RCTs are the criterion standard for evidence-based clinical recommendations (67), but performing such studies requires considerable resources. Studies of low-cost, nonpharmaceutical interventions such as elimination diets often lack the funding and organization of outside companies studying new drugs or of government-sponsored research (68). Consequently, many studies are small and poorly designed, making effective analysis of alternative treatments difficult, but given the popularity of dietary modifications among children with AD and their parents, there is incontrovertible value in reviewing all available evidence. The tremendous heterogeneity of dietary interventions and variability in trial designs—combined with the inherent weaknesses of many of these studies—precludes the development of a fortified thesis on the utility of dietary intervention in the treatment of AD. Despite these limitations, there is at least some evidence to support the use of elimination diets in specific, preselected populations. There is level I evidence that suggests that exacerbation of AD by true food allergies, as established by robust and validated testing, is a real phenomenon that medical practitioners can and should target. At the same time, evidence of the efficacy of elimination of specific foods in unselected patients without validated evidence of food allergy remains mixed at best.

Current evidence for strict elimination diets and caloric restriction remain discouraging. As tempting as it may be to take elimination diets to their logical extreme for refractory cases, it is clear that more radical interventions have significant potential for harm. Although some studies suggest more aggressive dietary interventions, these diets require intense oversight and are not feasible for most patients. More limited interventions eliminating less commonly studied foodstuffs such as artificial flavorings and sugar, although less risky, also lack supporting level I evidence and cannot be recommended. The exception

appears to be the use of low-metal diets in patients with proven metal allergies, which hold promise but must be further investigated to fully characterize their utility.

When contextualizing these studies, it is also important to note that any dietary intervention requires medical supervision and dietary counseling. The World Allergy Organization, the U.S. National Institute of Allergy and Infectious Disease, and the UK National Institute for Health and Clinical Excellence all recommend consultation with a dietitian when managing food allergies (69). Numerous studies have illustrated the risks of elimination diets in children; even limited elimination diets, such as avoidance of cows' milk, present a risk of calorie and nutrient malnutrition (70–72). Furthermore, some data suggest that elimination diets may weaken oral allergen tolerance and lead to more robust allergic reactions (including urticarial reactions, emesis, and anaphylaxis) upon allergen reintroduction (73,74).

Overall, these studies emphasize several well-established points of AD management and research. First, AD in children is known for its relapsing–remitting course, and many trials cannot exclude spontaneous resolution as the true cause for improvement. Thus appropriate follow-up and control groups are needed in all AD trials whenever possible. Second, dietary regimens are difficult to implement and adhere to for extended periods of time, especially in young patients and with increasingly strict diets. Feasibility and the importance of adherence in any dietary intervention should be discussed with patients and family members. Finally, the inherent difficulty of objectively assessing disease severity and the myriad factors that may influence AD severity, including environmental allergens and seasonal variations, complicate AD research. The weaknesses of the presented studies must therefore be considered within the larger context of the many challenges facing all AD trials.

Until a firm consensus is reached on the role of elimination diets in AD therapy, it is likely that public interest and attempts to use them without guidance will continue. Given that uninformed pursuit of elimination diets is not without cost to quality of life and may pose health risks, there is a pressing need for better RCTs. Although current evidence in the realm of dietary treatments for AD is lacking in quality, they may be of benefit to certain patients. Until then, we suggest these conclusions be interpreted not as an indictment but rather as a foundation upon which further investigations may be built.

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