

Food Allergies and Atopic Dermatitis: Differentiating Myth from Reality

CME EDUCATIONAL OBJECTIVES

1. Discuss the mechanisms behind food-related reactions.
2. Describe a systematic approach to the evaluation of food allergy.
3. Explain the relationship between IgE-mediated food allergy and atopic dermatitis.

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Adverse food reactions or food allergy can be the source of stress for many families. Some studies have assessed the quality of life for children with food allergy. One study showed that parents of children with food allergy report that family activities and general health perception are negatively affected.¹ Cohen et al, using principles established in measuring disease-specific, health-related quality of life instruments, found that multiple domains are affected in families with food allergy including school, camp, social activities involving food, vacations, children in the care of others, restaurant meals, and being near other children who are eating. Parents also reported anxiety and frustration over nutritional issues, worry over not being able to help their child with a reaction, and whether their child eventually will overcome the allergy.² Managing food allergy is an ongoing process involving cooperation between the parent and physician. Determining the etiology of food reactions can better guide therapies.³

Food allergies or adverse reactions to food can be defined in many different ways. A standard classification is used to split the reactions into non-immunogenic or immunogenic causes. Non-immunogenic reactions can be physical, toxic reactions

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(seafood contaminants), metabolic, infectious, or even pharmacologic in nature (increased use of caffeine).⁴ Immunologic reactions are based on the immune system's identifying the food protein antigen as foreign and starting an immune reaction. Among non-immunologic reactions, lactose intolerance is the most common and is caused by a deficiency in the enzyme lactase. This deficiency tends to cause an increase in lactose in the colon, which leads to excess gas production, abdominal cramps, flatulence, and diarrhea. Many patients with lactose intolerance classify themselves as "milk allergic," when in fact they react only to sugar found in milk and other foods, not milk protein itself. Other metabolic causes of symptoms resembling food allergy include glucose-6-phosphate dehydrogenase deficiency, pancreatic insufficiency, galactosemia, and phenylketonuria. The most common pharmacologic reactions are attributed to excess caffeine, tyramine in aged cheeses, and histamine, found in scombroid poisoning.^{5,6} A typical example of a toxic reaction is botulism food poisoning, in which the toxin interacts with the cyclic adenosine monophosphate regulatory protein. Other toxic reactions occur from ingestion of flavoring or preservatives, dyes, or contaminants, such as heavy metals or pesticides. Food poisoning from infectious sources is also considered in this category.

Immune-mediated reactions usually involve the gastrointestinal tract, the respiratory tract, and the skin. Immune reactions are divided into IgE-mediated and non-IgE-mediated. IgE-mediated responses to allergen exposure usually present as urticaria, flaring of atopic dermatitis, oral allergy syndrome, immediate gastrointestinal hypersensitivity, rhinorrhea, wheezing, or anaphylaxis. Non-IgE-mediated reactions are food specific T-cell mediated reactions, such as protein-induced enterocolitis, protein-induced enteropathy, eosinophilic proctitis, and dermatitis herpetiformis. There is also a mixed IgE and



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cell-mediated phenomenon found in eosinophilic esophagitis.

Food allergies are common, ranging from 1% to 6% in the general population depending on the study and population. Young children under the age of 3 have the highest prevalence at 6%.⁷ The prevalence decreases with age, because many children outgrow food allergies. Any food can cause an allergic reaction and the most likely foods vary with the prevailing diet. The most common foods causing food allergy are milk, egg, peanut, wheat, soy, tree nuts, fish, and shellfish.^{8,9} The natural history of food allergy also varies by the type of food and age of patient. For example, in infants with cow milk allergy who develop the allergy in the first year of life, 80% outgrow the sensitivity by 5 years.¹⁰ Sicherer also reported a similar finding for egg, soy, and wheat. Peanut, tree nuts, shellfish, and fish allergies are less likely to remit, with only about 20% of people reported to outgrow a peanut allergy.^{5,9}

It is important to understand the mechanism causing the food-related reactions, as it can help direct future therapies and management.

When a food allergen is ingested, it first passes through the gut barrier. The immu-

nologic food reactions represent an abnormal response to the mucosal immune system. The barrier in the gut comprises many factors that aid in rendering food antigens non-immunogenic, thereby inducing oral tolerance.⁶ The barrier is made up of tight junctions with epithelial cells covered by a mucus layer made up of chemical and cellular factors that aid in digesting and processing the food. After the food proteins are processed, antigen processing begins, and the food protein can enter the bloodstream through antigen-presenting cells on the mucosal barrier of the gut. Members of both the innate and adaptive immune systems are responsible for this process. It is postulated that intestinal epithelial cells, intestinal dendritic cells, and regulatory T-cells play a role in intestinal immunity and oral tolerance. The intestinal epithelial cells can process the antigen and present it to T-cells yet remain unresponsive to enormous amounts of antigen (ie, developing tolerance). It is thought that T-cells primed in the mucosal environment of the lamina propria are primed through the expression of IL-10 and IL-4 to induce tolerance.^{6,11-13} Without such a functioning barrier, we would react to everything we eat. Immaturity of this process is thought to lead to

TABLE.

Evaluation of Food Allergy

Suspect IgE-Mediated	Suspect Non-IgE-mediated	Suspect Non-immune
Broad screening should not be done without supporting history because of high rate of false positives	Consider biopsy of the gut	Consider hydrogen breath test
Skin prick testing	Consider patch testing	Consider sweat test
In-vitro testing for food-specific IgE		Consider endoscopy

the development of food allergy or adverse reaction to the food allergens.¹⁰ When tolerance is not achieved, the antigen-presenting cells further signal cytokines that cause either the production of IgE or trigger non-IgE mediated responses through cytokines such as IL-5. One study suggested that normal gut flora play a role in developing tolerance as well. Mice raised in a germ-free environment failed to have normal tolerance.^{6,14}

The gut barrier is important in immune tolerance and determining which ingested antigens are recognized as immunogenic. However, when that protective mechanism breaks down, the reaction to certain food antigens present in many different ways as described above. Why some reactions are IgE-mediated or non-IgE mediated remains poorly understood.

MECHANISM OF FOOD REACTIONS IN CHILDREN WITH ATOPIC DERMATITIS

Children with moderate-to-severe atopic dermatitis (AD) frequently have positive immediate skin tests or serum IgE directed to food allergens. During a positive challenge reaction, children have evidence of IgE response with higher plasma histamine concentrations, eosinophil granule products, and eosinophil activation markers. Some food-allergic children with chronic exposure to the food allergen were found to have an elevated basophil histamine release when compared to children without food allergy. However, some patients with AD have positive skin tests and negative food challenges. This implies that other arms of the immune system can regulate

the response.¹⁵ Also, the type of response depends on other factors. For example, casein (milk protein)-reactive T-cells that localize to the skin were found in higher concentrations in children with milk allergy and AD, when compared to milk-allergic patients without AD and to normal controls.^{16,17} Further research is needed to understand better the exact mechanism of food tolerance, localization of reactions, and induction of tolerance.

EVALUATION OF FOOD ALLERGY

History and Physical Examination

The patient’s history is one of the most important diagnostic tools for evaluation of suspected food allergy. A systematic review of the patient’s dietary history should be conducted, with particular attention to associations with the suspected provoking food: quantity ingested, symptoms, timing, reproducibility, treatment, and outcome (see Table 1).⁵ Additionally, aversion to specific foods may signal a potential reaction, as patients often intuitively refuse foods containing the allergen. It is also important to note whether other factors, such as exercise or alcohol ingestion, occurred around the time of food ingestion, as they can influence the absorption of food.¹⁸ The route of exposure can produce a variety of symptoms: cutaneous exposure can lead to contact urticaria, inhalation exposure can result in wheezing, and oral exposure can cause multiple symptoms (perioral, oral, dermatologic, respiratory, and gastrointestinal).¹⁹

In general, IgE-mediated food allergies occur soon after ingestion, typically within

minutes and usually within 2.5 hours. Multiple target organs can be involved.⁵ Non-IgE-mediated reactions typically manifest hours to days after the food is ingested; these reactions are more likely to involve the GI tract.⁶ If the reaction does not occur each time the suspected food is ingested, that particular food is less likely to be the trigger. When obtaining the history, it is important to note that details of the reaction are subject to recall. Also, trace amounts of foods may “contaminate” certain products, and “hidden ingredients” may be overlooked if labels are not read carefully.

A complete physical examination is required as evaluation of food allergy is pursued. The patient’s general nutritional status and any signs of chronic disease should be noted.

Testing for Food Allergy

With a thorough history and physical examination, suspected foods may be isolated. Based on history, the practitioner should narrow the etiology to an IgE-mediated, non-IgE-mediated, or non-immune-mediated process.

The standard skin prick test (SPT) is used for evaluation of IgE-mediated reactions. These skin tests can evaluate quickly the presence of food protein-specific IgE.⁵ A negative control, glycerinated saline diluent, is used to rule out nonspecific or dermatographic reactions. A positive control using histamine is placed to screen for the presence of residual antihistamines. A wheal at least 3 mm larger than the size of the negative control is considered positive.⁶ Positive responses depend on the release of endogenous histamine; thus, histamine-receptor-2 (H2) blockers may blunt the normal response. H1-blockers do not affect results as substantially. Additionally, prolonged systemic or topical steroid use may affect results as well.

Skin prick tests typically are done with commercial extracts. However, if the history is clear with a negative skin prick test, fresh food extracts can be used. Also, for

many fruits and vegetables, commercial extracts may not be adequate for skin prick testing because of the lability of the allergen. Often, fresh food must be used for skin testing in these cases.⁶ For any food, intradermal skin testing is not used, because of its nonspecificity and the increased risk for systemic reactions.

Positive skin prick testing indicates the presence of IgE antibody, and the positive predictive accuracy is approximately 50% depending on the food. Testing for a broad panel of foods not indicated by clinical history is not recommended, given the high rate of false positives. Negative predictive values for skin prick testing exceed 95% and exclude the presence of IgE-mediated food allergies.²⁰ Larger skin test reactions correlate with the likelihood of reaction, but do not correlate with the severity of reaction.⁶

In a prospective study by Sporik et al, data from 555 food challenges and skin prick tests on 467 children were evaluated. Based on this study, they were able to define skin wheal diameter at and above which a negative reaction did not occur. Open oral food challenges were positive with 100% specificity in children based on the following results: milk ≥ 8 mm wheal, egg ≥ 7 mm wheal, and peanut ≥ 8 mm wheal.²¹ However, since skin prick wheal and flare size can depend on the device used, additional work is needed to determine if this can be generalized in a larger manner.

In vitro methods also can be used to detect food protein-specific IgE. Generally, they are considered to be slightly less sensitive than skin tests.²² Specifically, immuno-CAP testing has been utilized in patients with persistent dermatographism, severe eczema, or when families are reluctant to discontinue use of histamine blocker medications that are needed to manage other comorbidities.⁵ In a prospective study of children and adolescents by Sampson, higher levels of food-specific IgE concentrations of egg, milk, peanut, and fish correlated with increased risk for clinical allergic reactions.²³

TABLE 2.

Food Specific IgE Levels and 95% Risk of Reaction

Food	Age Group	Serum IgE (KU/L)
Egg ²³	Child	≥ 7
Egg ²⁶	< 2 years	≥ 2
Cow milk ²³	Child	≥ 15
Cow milk ²⁷	< 2 years	≥ 5
Peanut ²³	Child	≥ 14
Fish ²³	Child	≥ 20

Celik-Bilgili et al conducted 992 controlled food challenges to cow milk, hen's egg, wheat, and soy in 501 children; 445 of the challenges were positive. Of those, 298 (67%) had early reactions, 63 (14%) had late reactions, and 84 (19%) had combined reactions. The most common manifestations of early reactions included urticaria, gastrointestinal, respiratory, and anaphylaxis. The late reactions were divided between worsening atopic dermatitis and gastrointestinal symptoms. Combined reactions consisted of worsening atopic dermatitis, gastrointestinal symptoms, and urticaria. The 95% predictive values for a positive reaction were only found for milk and egg. Similar to Sampson's work, 95% positive predictive values could not be found for wheat and soy. The specificity of specific IgE concentrations to the four foods was 69% to 97%, whereas the sensitivity was between 38% and 53%. However, information from each allergen and the age of the patient must be considered.²⁴

Roehr et al evaluated whether a combination of allergy tests could improve the prognostic value of positive food challenges. They studied 173 double-blind, placebo-controlled food challenges (DBPCFC) in 98 patients. All 98 patients underwent skin prick tests (SPT), atopy patch tests (APT), and allergen-specific IgE antibodies. The positive predictive value (PPV) for positive APT was high for cow milk (95%), hen's egg (94%), and wheat (94%), but 50% for soy. The SPT PPV for cow milk and hen's egg was 81%, 60% for wheat, and 50% for soy. Positive

APT showed good PPV. APT with specific IgE mildly elevated the PPV: 100% for cow milk protein and 94% for hen's egg. SPT with APT and specific IgE did not yield improved results. Using the tests to discriminate between early and late phase reactions were best predicted for cow milk with a combination of APT and specific IgE at any level. For hen's egg, early- and late-phase reactions were highly predictive using APT and specific IgE of 17.50 kU/L or specific IgE as a single test. An increase in PPV occurred with an increase in the levels of specific IgE, but the sensitivity dropped reciprocally.²⁵

Various groups have analyzed food-specific IgE levels to establish 95% risk of reaction in attempts to identify patients with increased probability of reacting during specific food challenges. These results are summarized in Table 2.

There are fewer diagnostic tests available for evaluation of non-IgE-mediated and mixed (IgE and cell-mediated) food allergy. Atopy patch testing remains one of the few testing modalities to evaluate such reactions.²⁸

ELIMINATION DIETS AND FOOD CHALLENGES

Elimination diets, in which suspected foods are removed, provide diagnostic information regarding food allergies. If an elimination diet is successful, food challenges are used to confirm the diagnosis of food allergy (see Table 1).⁵

Oral food challenges remain the gold standard to diagnose food allergies. Testing may be performed in different sce-

TABLE 3.

Food Allergy and Atopic Dermatitis Studies

Study	Number of Patients	AD Severity	Positive SPT or Positive IgE	Positive Food Allergy
Eigenmann et al ¹⁶	63 patients (median age 2.8 years)	8% mild 81% moderate 11% severe	65% with positive IgE	17% with positive food challenge
Eigenmann et al ²⁹	74 patients (median age 2.5 years)	46% mild 45% moderate 9% severe	55% with positive IgE	26% with food-induced anaphylaxis; 33.8% with food allergy
Hill et al ³⁰	487 patients	7% mild 7% severe	18% with positive SPT	In severe AD group, 69% had IgE-mediated food allergy (by SPT)
Garcia et al ³³	44 patients (mean age 7.5 months)	32% mild 64% moderate 4% severe	61% with food sensitization (based on positive SPT and/or specific IgE)	27% with positive food challenge

narios, such as open, single-blind, or DB-PCFC. These challenges should only be performed under strict medical supervision and in a setting properly equipped to treat potential severe reactions.⁵ Prior to scheduled food challenges, patients are asked to discontinue use of histamine blockers. The starting dose is kept low so as not to trigger a severe reaction. Doses are increased incrementally over 20 minutes. Once the goal dose is reached, patients are observed. Longer observation periods (approximately 4 hours) are required for non-IgE-mediated reactions.

FOOD ALLERGY IN ATOPIC DERMATITIS

The relationship between IgE-mediated food allergy and AD has been investigated extensively (see Table 3). Eigenmann et al conducted a prospective study to determine the incidence of IgE-mediated food allergy in patients referred for evaluation of AD. Serum IgE antibodies to milk, egg, wheat, soy, peanut, and fish, determined by CAP immunoassay were studied in 63 patients (median age 2.8 years). Severity of AD in the study population included five patients with mild disease, 51 patients with moderate disease, and seven patients with severe disease. Forty-one patients had positive specific IgE values, while 22 patients had negative values. Of the 41 patients with positive IgE values, 19 underwent food challenges (10 patients

were lost to follow-up). Eleven of the 19 patients had positive food challenges, with 94% exhibiting skin reactions. There were no episodes of anaphylaxis. Overall, 23 of the 63 patients (37%) exhibited clinically significant IgE-mediated clinical reactivity to food, as determined by food-specific IgE antibody levels, a convincing history and food-specific IgE and/or prick test, or CAP immunoassay greater than 95% predicted cut-off. This study concluded that in patients with refractory, moderate-severe atopic dermatitis, evaluation for food allergy should be pursued, as this subset of patients has a higher prevalence of food allergy than the general population.¹⁵

Another study by Eigenmann et al evaluated 74 Swiss children (median age 2.5 years) with AD for the prevalence of food allergy. Severity of AD included: 34 with mild disease, 33 with moderate disease, and seven with severe disease. Initially, patients were skin prick tested to common food allergens (milk, egg, peanut, wheat, soy, fish, and nuts) and to other suspected foods based on clinical history. Thirty patients had negative SPT. Those patients who were positive to causative foods were evaluated further by specific serum IgE antibodies (CAP system). Nineteen patients were diagnosed with food-induced anaphylaxis based on clinical history and/or CAP values above the 95% PPV. Forty-three food challenges were conducted for patients with positive SPT, but inconclu-

sive CAP results (between the 95% NPV and 95% PPV). Six of those patients had positive food challenges. Altogether, food allergy was noted in 33.8% of the study group, with egg, milk, and peanut being the most common causative foods.²⁹

The relationship between AD and IgE-mediated food allergy in infancy was examined in a study by Hill et al. A cohort of 487 infants was followed from age 6 months to 1 year. Within the group, 141 (29%) were classified as having atopic dermatitis (based on 8 days or more of topical steroid use). The severity of AD in the group was determined based on topical steroid use: 36 patients had "mild" AD, 35 patients had "severe" AD, and the remaining patients were considered to have "moderate" AD. Ninety patients were noted to have IgE-mediated food allergy, based on skin prick testing (82% to egg, 35% to peanut, and 17% to cow milk). Approximately 56% of these patients were categorized as having AD. Furthermore, they reported that the prevalence of IgE-mediated food allergy increased as the severity of atopic dermatitis increased. For the group with severe AD, 69% had IgE-mediated food allergy (by SPT).³⁰ However, the diagnosis was not confirmed by food challenges. Because the food positive rate is approximately 50% for skin prick test, the actual number of patients may be up to half of the total.

Monti et al performed a prospective study of 107 patients aged 1 to 19 months

with atopic dermatitis who had never ingested egg. The goal was to compare the outcome of a first oral challenge to egg (clinical reaction) with the results to albumen and yolk SPT and RASTs. Thirty-eight percent had mild eczema, 34% had moderate eczema, and 28% had severe eczema. Seventy-two (67%) of the patients enrolled had a positive egg challenge. During the challenge, skin reactions including urticaria, erythematous or macular rash were most frequent (85%). Re-exacerbation of eczema occurred in 17%. Other reactions included gastrointestinal, respiratory, ocular, and cardiovascular (37.5%, 18%, 5.5%, and 1%, respectively). They then evaluated how the skin test and CAP RAST test predicted a positive challenge. When the wheal of the albumen (egg white) and yolk SPT was more than 5 mm, the challenge result was positive. The specificity of a 4 mm wheal was 91% for albumin and 94% for yolk; and 86% and 89% for a 3 mm wheal, respectively. On the other hand, the sensitivity for SPT for the 3 mm wheal was the highest and declined for the 4 mm and 5 mm wheals. Of the five children with severe reactions during a challenge, three had a 5 mm wheal to albumen, but not yolk. The challenge was always positive when the CAP RAST was greater than 99KU/L for albumen and greater than 17.5 KU/L for yolk. The five children with severe reactions had negative CAP RAST values. Forty percent of children who reacted displayed values equal to or higher than cut-off values in four or more tests.³¹

In a multicenter, international study by Hill et al, 2,184 subjects (mean age 17.6 months) with atopic dermatitis were studied (Table 3, see page 88). Sixty-eight percent of these patients were noted to have moderate-severe eczema. Patients were classified as having “high-risk IgE food sensitization” (HR-IgE-FS) if their CAP RAST measurements exceeded the 95% PPV for specific foods. These patients had no reported adverse reactions to foods or no reported exposure to the foods. There

was a statistically significant association between the age of AD onset and HR-IgE-FS. Of the children with HR-IgE-FS, 99% were to egg, 25% to cow milk, and 11.5% to peanut. Furthermore, there was an association between AD severity and history of urticaria; there was an increased risk of urticaria with sensitization. The authors concluded that, for children with AD, the earlier the age of onset and the greater the severity, the more likely it was for patients to have high levels of IgE-mediated food sensitivity. Sensitivity to milk, egg, and/or peanut were greatest in patients whose AD developed in the first 3 months of age.³²

Garcia et al reported a high prevalence (61%) of food sensitization in a study of 44 infants (mean age 7.5 months) with AD. The severity of AD included 32% with mild disease, 64% with moderate disease, and 4% with severe disease. Food challenges were conducted for cow milk on all patients after 1 month of elimination. Additionally, patients with positive food-specific IgE or positive SPT underwent food challenges; milk was eliminated from the diet for 1 month and other causative foods were eliminated from the diet for 2 weeks. Twenty-seven percent of the cohort had positive food challenges. In the cohort, food sensitization (based on positive SPT and/or food-specific IgE greater than 0.35 kU/L) was noted in 61% of the study population. Further delineating based on AD severity and food sensitization (positive SPT and/or positive food specific IgE) was noted in 43% of those with mild atopic dermatitis, 68% of those with moderate atopic dermatitis, and 100% of those with severe atopic dermatitis. This study showed that egg was the most commonly implicated food, noted in 61% of the study population.³³

Thompson et al enrolled 23 patients from a tacrolimus study in a survey documenting the observations of parental concerns of food allergy as a cause for pediatric eczema. The majority of patients had moderate to severe eczema. Seventy percent had positive skin tests, and 30% had

definite immediate IgE-mediated reactions to food. However, as the skin improved, the number of eczema flares in a 6-month period went from 25 + 23 to 5.2 + 5.³⁴

Multiple studies have shown that approximately 30% of patients with severe atopic dermatitis have food sensitization. Addressing food allergies and initiating elimination diets have led to improved skin symptoms in these patients. Specifically, in a study by Sampson and McCaskill, 113 patients with severe atopic dermatitis and food allergies were evaluated with DBPCFC. Sixty-three children (56%) had positive food challenges; 84% of these children developed skin symptoms.; 72% of the reactions noted were attributed to egg, peanut, and milk. Approximately 40% of the 40 patients who were reevaluated after appropriate elimination diets were initiated showed loss in food hypersensitivity after 1 to 2 years.³⁵

Another study by Sampson et al reviewed patients with atopic dermatitis and food hypersensitivity who had initiated elimination diets. After 1 year, 25% of the 75 patients in the cohort lost signs of clinical food hypersensitivity, based on DBPCFC evaluation. After 2 years, DBPCFC was repeated, and four of 44 remaining patients lost their clinical food hypersensitivity. They also found that those patients who only developed skin symptoms during the initial evaluation were most likely to lose their food hypersensitivity.³⁶

MANAGEMENT

The only proven therapy for food allergy is complete avoidance of the specific food trigger.⁵ However, dietary elimination must be implemented with caution, as patients may be at risk to develop nutritional deficiency. The Food Allergy Network (www.foodallergy.org) provides comprehensive resources for patients. Education is essential to help identify avoidable risks. Patients must be trained to read food labels carefully to avoid any accidental ingestion of causative foods. Furthermore, patients should be advised to avoid buffets, given

the high likelihood for cross-contamination of offending allergens.

All patients at risk for anaphylaxis must be taught to identify symptoms early and quickly. Furthermore, they must be prepared to treat reactions appropriately with the use of auto-injectable epinephrine within minutes after an allergic reaction. Delayed use of epinephrine has been associated with an increase in biphasic reactions and the risk of a fatal reaction.¹⁹

CONCLUSION

Several studies have shown that approximately 35% to 40% of children with moderate-to-severe AD have food allergy. Sampson et al found that cutaneous reactions during food challenges were generally eruptions in sites affected by AD.¹⁰ Some studies suggest that AD affects 10% of children sometime in their life. Guillet et al found that younger age of the patient and greater severity of AD were directly correlated with the presence of food allergy. Some studies show that AD can be partially treated by removing the allergenic food from the diet,³⁷ but treatment should be combined with optimal atopic skin care and appropriate pharmacologic therapies when needed. It is well established that atopic dermatitis is exacerbated by food allergy. Diet elimination and good skin care have shown to improve outcomes. Since the prevalence of food allergies and AD decrease with age, close follow-up can help families determine when to reintroduce foods into the diet.

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