

## Unnecessary Milk Elimination Diets in Children with Atopic Dermatitis

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**Abstract:** Milk elimination diets are frequently adopted in the treatment of atopic dermatitis, although the real prevalence of clinically relevant food allergy remains unclear and reports from different authors are often in disagreement. We investigated the percentage of children allergic to cow's milk compared with the rate of milk exclusion diets in a group of patients with atopic dermatitis. We enrolled 206 children (79 girls, 127 boys), mean age 45.8 (4–68) months, affected by atopic dermatitis into our study. All children underwent radioallergosorbent test for casein, alpha-lactalbumin and beta-lactoglobulin, prick test, atopy patch test, and oral provocation test. Children were followed up at 1, 3, 6, and 12 months. Of the 206 patients, 20 were excluded from statistical analysis, leaving 186. Forty-five (24.2%) were on a milk elimination diet and 141 on a normal diet. Four patients on the milk-free diet (8.9%), accounting for 2.2% of all patients, were found to be allergic. In the others, milk reintroduction did not cause the disease to worsen during the follow-up period. No children on a normal diet were found to be allergic. Our results demonstrated an actual prevalence of cow's milk allergy in patients on milk elimination diets (4%) to be significantly lower than the number of patients prescribed such diets (24.2%)—confirming that this measure is being applied excessively.

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Atopic dermatitis (AD) is an inflammatory, chronic-relapsing dermatosis, affecting approximately 10–12% of children (1). Although its pathogenesis is still unknown, AD is considered a multifactorial disease triggered by the interaction of genetic and environmental factors (food, airborne allergens, infectious agents) (2). During early infancy, food allergens are considered particularly important. In fact, a high percentage of children with atopic dermatitis show food-specific circulating IgE and positive prick tests (3,4). Experimental data show that IgE is involved in immediate and delayed hypersensitivity-induced reactions, playing a crucial role

in antigen processing and in the activation of T lymphocytes by antigen-presenting cells (5). Despite the fact that experimental and laboratory evidence indicate that food allergens play a pathogenetic role in a subgroup of patients, the real prevalence of clinically significant allergies in atopic children still remains an open question (1). The relationship between atopic dermatitis and food allergy has been discussed for a long time. According to a recent review by Fiocchi et al, at least 15 studies from 1975 to 2003 have explored the efficiency of exclusion diets in children with atopic dermatitis (3). We observed in clinical practice that only in exceptional instances did

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food elimination in allergy-test positive patients lead to short- and long-term significant improvement.

No standard guidelines are currently available regarding the use of the allergologic tests [radioallergo-sorbent test (RAST), prick test, and atopy patch test] in children with atopic dermatitis and their significance and consistency (6). Although the oral provocation test, open or double blind, is the only test capable of diagnosing food allergy, it is complex, expensive, and not risk free. Hence, it should be carried out only in highly selected patients (7).

We focused on cow's milk allergy, which certainly represents a paradigmatic situation given its supposed frequency among foods. It is considered one of the foods most frequently responsible for allergies, followed by eggs, wheat, and soy (8,9). The principal aim of the study was to assess the real rate of clinically significant milk allergies in a group of consecutive patients with atopic eczema followed up for 1 year, and to compare it with the rate of prescribed milk-elimination diets in the same group of patients. Our results confirmed a significantly low incidence of cow's milk allergy, especially when compared with the high rate of milk-free diets prescribed. This suggests that these diets are overprescribed in our region, often without adequate allergologic evaluation.

## PATIENTS AND METHODS

### Patients

For our study, we examined 206 consecutive patients (79 girls, 127 boys, mean age 45.8 months (median 24, range 4–68), mean SCORAD 28.2 (median 32.2, range 11.1–64.5) with atopic dermatitis (diagnosed according to the Hanifin/Rajka criteria) (10) referred to the Pediatric Dermatology outpatient center of our institution during 2001–2003. Of these, 186 were included in the statistical analysis of results.

All patients underwent clinical examination, family and personal history data were collected, and the SCORAD index was calculated according to the European Task Force on Atopic dermatitis guidelines (11). A SCORAD index of <25 was considered to indicate a mild disease, an index between 25 and 50 to indicate moderate disease and an index of >50 to correlate with severe disease. For each patient, informed consent was given. All patients underwent a specific IgE assay (specific IgE UniCAP-FEIA RAST; Pharmacia Diagnostics, Uppsala, Sweden) for casein, alpha-lactalbumin, and beta-lactoglobulin, and a prick test and atopy patch-test for cow's milk.

A selected group of patients also underwent an open oral provocation test (OPT) when at least one of the following criteria existed:

- Existing milk-elimination diet at the time of first visit.
- Resistance to food reintroduction on the part of the parents or pediatrician despite the negative results of test.
- At least one markedly positive test result (RAST > class 3, prick + + +, atopy + + +).
- At least two low titer positive tests.

When an OPT result was positive, a double-blind placebo-controlled food challenge (DBPFC) was performed. In all patients, except those challenge positive, cow's milk was reintroduced into the diet. Children underwent a follow-up visit at 4 weeks, 6 months, and 1 year after milk reintroduction. At each visit, data on the disease course were collected and the SCORAD index was calculated. All parents were carefully informed about the importance of a correct application of the topical therapy.

### Prick Test

Prick tests were carried out following the prick by prick method with fresh foods. Systemic antihistamines were withheld 72 hours before prick testing. The test was carried out as follows: the skin of the volar part of the forearm was disinfected and a droplet of the fresh food was applied. With a sterile 1 mm lancet the skin superficial layers were pricked through beneath the droplet, in order to make the allergen penetrate. The drop was immediately dried after puncture. The reading was carried out at 15 minutes, and the test was considered positive when a 3 mm or larger pomphous reaction appeared with no reaction to the negative control (NaCl 0.9%). The evaluation of the skin response degree was made with reference to the wheal produced by the positive control with histamine. Considering the extent of the histaminic wheal equal to 1, the evaluation was carried out as follows: 1/4 to 1/2 wheal = +, 1/2 to 1 wheal = + +, 1 to 2 wheal = + + +, >2 wheal = + + + +. In our study, prick tests were considered positive with a wheal that was at least 1/4 of the histaminic wheal.

### Atopy-Patch Test

The test was performed on healthy skin (the back), after a 1-week discontinuation of systemic anti histaminic therapy. One drop (50  $\mu$ l) of cow's milk was put in 12 mm Finn chambers, on blotting paper disks. The result of the test was read at 48 and 72 hours after removal of the disk. Positive reactions were vesicular eczema-like reactions, and appearance of edema, papules, or blisters on the allergen application site. The

reaction was considered to be positive when one of the following conditions was found: erythema = +, erythema, edema = ++, erythema, edema, blisters, or papules = ++++, confluent blisters = +++++. Irritant reactions were not considered as positive.

### Food Challenge

The OPT was performed following the method suggested by Niggemann et al (12): discontinuation of antihistamines at least 72 hours before the test is performed, evaluation of the SCORAD index at day 1, administration of increasing food doses (0.1, 0.3, 1, 3, 10, 30, 100 mL) at 20-minute intervals, discontinuation of the test at the appearance of immediate hypersensitivity symptoms (vomiting, urticaria, anaphylactic shock, angioedema), patient observation for 120 minutes after last administration, control of patient at 24 and 48 hours after food challenge.

The test was considered positive if an immediate hypersensitivity reaction occurred or eczema exacerbation (SCORAD index at least 20 points higher than the initial value) occurred at day 3.

For DBPCFC, a similar procedure was adopted, but the randomization was performed by a dietician (cow's milk vs. Neocate). The challenges were performed at 4-week intervals.

## RESULTS

Out of 206 patients, 18 were lost to follow-up and excluded from statistical analysis. Two other patients on the diet were excluded from the study because their parents refused OPT although the allergy tests were negative.

A total of 186 patients continued the investigations. Among these, 45 (24.2%) were on milk-elimination diets at the time of their first examination and 141 (75.8%) were on a normal diet.

One hundred sixty-two (87.1%) patients were monosymptomatic (absence of respiratory or gastrointestinal symptoms), and in 168 (90.3%) the parents did not link milk consumption and skin disease. In the vast majority of patients on the milk-free diet (39/45; 86.6%),

milk exclusion was prescribed by a physician (usually a pediatrician), in 26/45 (57.7%) without any prior allergy evaluation, and in 16/45 (35.5%) after a positive RAST. Only 3 of 45 (6.66%) had a complete allergy evaluation before starting the diet. No significant difference was found between the two groups of patients regarding the severity of their AD.

Among the patients on the diet, four (8.9%) were found to be allergic (positive OPT, confirmed by DBPCFC). Milk allergy was excluded in the other patients, and milk was reintroduced into their diet.

No patient in the nondiet group was found to be allergic to milk. The total percentage of allergic patients in our sample was 2.2%. Baseline data of the study group are summarized in Table 1.

At follow-up, no patients showed a worsening of AD on reintroduction of milk into their diet. On the contrary, the accuracy of treatment led to a 23.2 (range 12–36.2) point average decrease in the SCORAD index.

The course AD showed a positive trend in 82% of patients at the 3-, 6-, and 12-month follow-up. In the remaining patients, the disease remained stable and was not marked by uncontrolled phases in relation to milk reintroduction (omitted data).

### RAST Results

One hundred twenty-eight patients (68.8%) were RAST negative and 45 (24.2%) were low titer positive (class 1 or 2). Only 13 patients (7%) were found to be RAST positive class 3 or higher. Of patients on exclusion diet, 46.7% were RAST negative versus 75.9% of patients not on a diet. All allergic patients were class 3 or higher. None of the nonallergic patients had a RAST higher than 3 (Table 2).

### Prick Test Results

Analyzing all patients, prick tests were negative in 155 (83.3%) and positive in 31 (17.7%). Prick tests were negative in 32 (71.1%) patients on milk elimination diets and in 120 (85.1%) patients on a regular diet. Relative data are summarized in Table 3.

**TABLE 1.** Baseline Data of the Study Group of Allergic and Nonallergic Children

|                      | Allergic milk exclusion diet | Nonallergic         |                | All patients |
|----------------------|------------------------------|---------------------|----------------|--------------|
|                      |                              | Milk exclusion diet | Nondiet        |              |
| Number, mean (range) | 4                            | 41                  | 141            | 186          |
| Age (months)         | 40.1 (10–68)                 | 38.2 (8–60)         | 42.3 (4–48)    | 45.8 (4–68)  |
| SCORAD               | 27.9 (12–64)                 | 29.1 (11–62.5)      | 26.5 (15–62.1) | 28.2 (11–64) |
| Sex (F/M)            | 2/2                          | 18/23               | 49/92          | 69/117       |

**TABLE 2.** Frequencies [*n* (%)] of Patients on Exclusion or Normal Diet, Grouped by RAST Results

| Patient's food | RAST       |           |           |           |          |         |
|----------------|------------|-----------|-----------|-----------|----------|---------|
|                | Class 0    | Class I   | Class II  | Class III | Class IV | Class V |
| Exclusion diet | 21 (46.7)  | 7 (15.5)  | 6 (13.3)  | 9 (20)    | 1 (2.2)  | 1 (2.2) |
| Nondiet        | 107 (75.9) | 14 (9.9)  | 18 (12.8) | 2 (1.4)   | 0 (0)    | 0 (0)   |
| Total          | 128 (68.8) | 21 (11.3) | 24 (12.9) | 11 (5.9)  | 1 (0.5)  | 1 (0.5) |

**TABLE 3.** Frequencies [*n* (%)] of Children on Exclusion or Normal Diet, Grouped by Skin Prick Test and Atopy Patch Test Results

| Patient's food | Prick test |           | Atopy patch test |           |
|----------------|------------|-----------|------------------|-----------|
|                | Neg        | Pos       | Neg              | Pos       |
| Exclusion diet | 32 (71.1)  | 13 (28.9) | 29 (64.4)        | 16 (35.5) |
| Nondiet        | 121 (85.8) | 20 (14.2) | 126 (89.4)       | 15 (10.6) |
| Total          | 153 (82.2) | 33 (17.7) | 155 (83.3)       | 31 (16.7) |

**TABLE 4.** Frequencies [*n* (%)] of Patients, on Exclusion or Normal Diet, Who Showed all Examinations Negative (A); One Positive Examination at least (B); Two Positive Examinations (C); Three Positive Examinations (D)

| Patient's food | A         | B         | C         | D        | All patients |
|----------------|-----------|-----------|-----------|----------|--------------|
| Exclusion diet | 9 (20)    | 14 (31.1) | 17 (37.8) | 5 (11.1) | 45 (24.2)    |
| Nondiet        | 84 (59.6) | 47 (33.3) | 10 (7.1)  | 0 (0)    | 141 (75.8)   |
| Total          | 93 (50)   | 61 (32.8) | 27 (14.5) | 5 (2.7)  | 186 (100)    |

### Atopy-Patch Test Results

Atopy-patch test results were negative in 155 patients (83.3%) and positive in 31 patients (16.7%). Considering the two groups of patients, the test was negative in 29 (64.4%) patients on the diet and in 126 (89.4%) nondiet patients. Relative data are summarized in Table 3.

### Test Concordance

Of patients following the milk-free diets, nine (20%) of them had negative tests results, versus 84 (59.6%) non-diet patients (31.1%). Only five patients (2.7%) had three positive test results. Four of these patients were on the diet and were found allergic to milk. Relative data are summarized in Table 4.

### OPT Results

Open oral provocation tests were performed on 60 patients, of whom only four (6.6%) had positive results and underwent DBPCFC, confirming the results of OPT. In all other patients, the excluded food was reintroduced into the diet.

### DISCUSSION

Cow's milk is considered one of the foods most frequently responsible for allergic reactions in children with

atopic dermatitis (9). Even though we tested our study children for other common food allergens such as eggs, wheat, fish, peanuts, and soy, this study focused exclusively on cow's milk, due to the high number of children who were following a cow's milk elimination diet at the time of the first examination, often without a correct allergy evaluation.

The true prevalence of food allergies among children with AD is still under discussion. Sampson and McCaskill found a food allergic reaction in 60% of children (13), while Burks et al (14) found a reaction in 33%. Novembre and Vierucci (15) reported that 37% of their patients had cow's milk allergy/intolerance. We found an extremely low rate of cow's milk allergy (2.2%), markedly lower than the percentage of patients on a milk-free diet (24.2%). Considering only the group of patients on a diet, the percentage of allergic patients was lower than 9%. This was similar to the percentage reported by Eigenmann in a group of pediatric dermatology patients in whom, despite that overall 37% had food allergies, cow's milk was responsible for allergy in only 3 of 63 patients (4.7%) (1). It is important to consider that, in all the studies mentioned above, patients were selected on the basis of a positive clinical history, while our population included consecutive, nonselected children. The low rate of allergic subjects in this study could be related to the low mean SCORAD index, but we decided not to exclude patients on a milk-free diet with low SCORAD indexes; with the assumption that a

favorable course of the disease might be attributed to milk avoidance. Even though the median age of our study patients was low (24 months), we included children older than 5 years in our study (an age in which food allergies are not so common) who were still following a milk exclusion diet. Of interest, one of the confirmed allergic children was 6 years old, and had a SCORAD index of 11.6 at the first visit.

The specific IgE assay has a high negative predictive value, despite a very low positive predictive one. Recently, more importance has been attributed to serum specific IgE levels in predicting food allergy. Sampson calculated a 90% positive predictive value when milk-specific IgE concentrations are equal to or higher than 23 kU/L (class IV) (17). According to Garcia-Ara et al, in young children a 90% positive prediction power was found for concentrations equal to or higher than 2.5 kU/L (class III) (18). Low specific IgE levels may have no clinical significance and represent a normal phenomenon, especially in early childhood (19).

In our study, RAST was positive in 53.3% of the patients on a milk-free diet and in 34% of nondiet patients, but only two patients had a class IV or higher RAST test. All allergic patients had a class III or higher RAST.

Prick test predictivity has long been studied. According to Sampson and Albergo, a  $> 3$  mm reaction is highly predictive for food allergy (20), while for Atherton, SPT have little value in identifying foods that are responsible for allergies (21). In our study, prick tests were negative in 82.2% of patients and positive in 17.7%.

The usefulness of patch tests in diagnosing food allergies is still controversial. According to Roehr et al (8), the combination of the APT result and specific IgE values higher than 3.5 kU/L would reduce the need for challenge tests. Some studies showed promising results on APT (8,22) that were not confirmed by others (23). In our sample, patch tests were negative in 83.3% of patients and positive in 17.7%. These results do not allow us to draw any conclusions about the possible usefulness of APT in diagnosing food allergies. One half of the patients in our study had negative tests; 32.8% had only one positive test; 14.5% had two positive tests and only 2.7% had all positive tests.

Despite the fact that the percentage of patients with at least one positive test was significantly higher (80%) among children on a milk-free diet, 20% of these patients had negative tests. In these instances food elimination was probably only prescribed "ex-adiuvantibus," without any laboratory indications. All allergic patients had a class III or higher RAST test, positive SPT ( $> ++$ ), and positive APT ( $> ++$ ). This complies with Sampson's

view (17) about the predictive value of specific IgE concentrations.

In a recent review, Host et al stated (6) that allergy tests should be performed only in patients with severe or persistent disease, multiple symptoms, resistance to treatments or to sun exposure, or highly suspect clinical histories.

Furthermore, food allergy can be diagnosed only on the basis of strict and well defined criteria (5,6): a significant reduction of symptoms following elimination of a suspect food, exacerbation of symptoms after triggering tests, and their disappearance after re-elimination of that food.

On this basis, we can say that the criteria to rule out food allergy in the great majority of our patients may already have existed, and were sufficient to avoid additional allergy tests, greatly reducing social and health-care costs. Unfortunately, the belief that atopic dermatitis is almost always caused by cow's milk allergy is deeply rooted, as shown by the fact that, in our study, for some children on a milk-free diet with all negative tests, milk was reintroduced only after the OPT. Furthermore, in two children on milk-free diets who had a low SCORAD index and negative tests, it was not possible to perform the OPT due to the fact that their parents reported strongly positive clinical histories. Because it was not possible to perform the OPT we could not include these patients in our series.

According to a recent review by Fiocchi et al (3), most studies on diet restrictions in children with atopic dermatitis only explored short- and medium-term effects. Only one recent work (24) evaluated the positive diet results at 12 months. In our study all patients were followed up for 1 year, and we observed that in 82% of patients, the disease had a positive course after the adoption of adequate topical therapy (omitted data). In the remaining patients, the disease was stable and did not show uncontrollable flares in relation to the reintroduced food. This confirms the importance of good therapy that includes the use of emollients and topical corticosteroids to keep skin xerosis and the skin barrier alterations under control that are crucial in AD pathogenesis (16).

Even if a milk elimination diet is still considered a pivotal decision in the treatment of children with atopic dermatitis, it must be remembered that a food allergy diagnosis can have a strong social and economic impact and affect the psycho-physical development of a child. The exclusion of one fundamental food must be decided on only after careful evaluation of allergy tests and only after considering the child's clinical history. Although our results show that the frequency of cow's milk allergies in children with AD is probably overestimated, many aspects of the

complex relationship between AD and food allergens remain unclear.

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