



# Pancreatic Enzyme Supplementation in Patients with Atopic Dermatitis and Food Allergies: An Open-Label Pilot Study

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## Abstract

**Background** Atopic dermatitis (AD) is a chronic inflammatory skin disease that affects both patients and their families. Current therapies often alleviate symptoms but do not prevent or eradicate the disease.

**Objectives** Our objective was to determine whether pancreatic enzyme supplementation is an effective and safe treatment in refractory pediatric AD associated with food allergies.

**Methods** We conducted an open-label pilot study using a case–control design. Patients with severe AD and known food allergies refractory to conventional therapies and exclusion diets were recruited and treated for 6 weeks with oral supplementation of pancreatic enzymes. The primary endpoint was the severity of AD, using the Scoring Atopic Dermatitis (SCORAD) index. Secondary measures included markers of intestinal permeability (urinary sucrose and lactulose/mannitol excretion).

**Results** A total of 11 patients met all eligibility criteria and completed the trial. Significant improvement in AD was observed after 6 weeks of pancreatic enzyme supplementation (SCORAD index  $52.3 \pm 5.5$  vs.  $34.6 \pm 7.6$ ;  $p = 0.0008$ ). Beneficial effect was observed in 9 of 11 patients, without adverse events. Fractional urinary sucrose excretion improved to a level comparable to that of age-matched controls ( $p < 0.05$ ). However, urinary lactulose:mannitol ratios remained abnormally high compared with those of controls ( $p = 0.01$ ).

**Conclusions** Pancreatic enzyme supplementation was associated with improved AD and gastroduodenal permeability. Additional randomized placebo-controlled studies are required before this treatment can be recommended in this clinical setting.

## Key Points

Abnormal intestinal barrier function was observed in children with atopic dermatitis (AD) and food allergies, supporting the hyperpermeable gut as a contributing factor to pathogenesis.

This is the first study supporting pancreatic enzyme supplementation in patients with AD with food allergies, as pancreatic enzyme supplementation resulted in significant clinical improvement.

In children with severe AD and food allergies, the observed association between pancreatic enzyme supplementation and improved gastroduodenal permeability is novel.

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## 1 Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin condition that affects more than 10% of children, making it the most common pediatric skin disease worldwide [1–5]. AD significantly affects the quality of life of both patients and their families, and recent studies reveal strong associations between AD and mental health disorders, poor school performance, and family dysfunction [5–8].

AD is generally characterized by fluctuating periods of relapse and remission. Most first-line treatment algorithms for preventing relapses are based on topical hydrating therapies and avoidance of provocation factors [9–11]. Exacerbation management usually requires an anti-inflammatory treatment, with topical corticosteroids as the cornerstone therapy and topical calcineurin inhibitors (tacrolimus and pimecrolimus) as effective second-line therapies [12–14]. Systemic anti-inflammatory treatments such as immunomodulators (methotrexate and azathioprine) are indicated for severe or refractory cases, whereas systemic corticosteroids are generally not recommended in pediatric patients because of the associated long-term side effects and the high risk of relapse after discontinuation [9, 15, 16]. Although current therapies usually provide symptom relief, they do not prevent or eradicate the disease. In addition, the disease follows a more aggressive course in patients with moderate-to-severe AD, making management difficult [17].

Numerous studies have suggested that multiple, often unrecognized, food allergies are frequently implicated in the pathogenesis of AD [18–22]. Food allergies are more likely in severe AD refractory to standard therapy [1, 5, 21, 23]. More than 30% of toddler-age children with moderate-to-severe food allergies have AD, and food allergens may provoke flares of AD in sensitized individuals [3, 24–28]. Allergen avoidance, antihistamines, mast cell stabilizers, and topical steroids or tacrolimus fail to control symptoms in severe cases.

Children with AD often have increased intestinal permeability [29]. Duodenal biopsies have shown increased intestinal permeability to augment antigen transfer across the gut mucosa, contributing to immune responses to food allergens and food-related AD flares in sensitized individuals [30]. Moreover, a correlation has been established between intestinal hyperpermeability and exocrine pancreatic dysfunction [31]. Eosinophilic infiltration of the intestinal mucosa is commonly observed in milk-allergic children with severe AD. Allergic (eosinophilic) colitis is rarely seen after infancy [32], partly because of the maturation of pancreatic exocrine function allowing for more complete hydrolysis of food allergens in the small bowel [19, 33]. Similarly, AD flares to common food allergens are seen much less frequently in adults than in children [24, 25].

We hypothesized that unknown allergens can induce intestinal inflammation and disrupt the mucosal barrier, resulting in excessive intestinal permeability to luminal proteins in children with severe AD refractory to standard medical therapy. The major aims of this study were to (1) determine whether pancreatic enzyme supplementation is effective and safe in the treatment of children with refractory AD associated with food allergies, (2) investigate whether skin lesions correlate with excessive intestinal permeability, and (3) establish whether the clinical improvement subsequent to pancreatic enzyme supplementation is reflected by reduced intestinal hyperpermeability.

## 2 Patients and Methods

Patients (aged 1–18 years) were recruited from the Pediatric Dermatology Clinic at Sainte Justine Hospital if they met the following two criteria: (1) AD, as defined by Hanifin and Raika [34], refractory to conventional treatment (including avoidance of established food allergens for each patient, emollients, topical corticosteroids, mast cell stabilizers) for at least 4 months; and (2) type I (immunoglobulin E [IgE]-mediated) food allergies demonstrated by clinical history and supported by positive skin prick tests and/or serum IgE testing to specific food allergens by enzyme allergosorbent test [32]. Patients were excluded if they had any active skin infection requiring topical or systemic antibiotics in the 2 weeks before screening. Patients with known inflammatory bowel disorders such as Crohn's disease, ulcerative colitis, or celiac disease were also excluded, as were patients with other systemic diseases. Any modification of topical or systemic treatment during the 2 weeks before screening was also an exclusion criterion.

The severity of the AD was assessed by a dermatologist using the Scoring Atopic Dermatitis (SCORAD) index [35], a validated objective measure of the extent and intensity of AD lesions. It also evaluates the patient's subjective symptoms such as itchiness and sleeplessness using a visual analog scale. Intestinal permeability was measured using standard probes: urinary sucrose excretion, known to correlate with abnormal gastroduodenal permeability [36–38], and the urinary lactulose:mannitol ratio, where an increased ratio ( $>0.3$ ) is indicative of abnormal small bowel permeability [39]. These probes were measured by high-performance liquid chromatography in a 5-h urine collection after an overnight fast. Consenting age-matched healthy controls ( $n=8$ ) without a history of AD or food allergies, recruited from the Orthopedic clinic, underwent intestinal permeability testing, as described.

After these baseline evaluations, patients received pancreatic enzyme supplements for 6 weeks. Children aged  $<7$  years received the contents of a single capsule

containing 37,500 units of proteases (Creon 10<sup>R</sup>, Solvay Pharma) with each meal and one-half of a capsule with snacks. The dose was doubled for older patients. A repeat SCORAD assessment and intestinal permeability testing were carried out at the end of the 6-week treatment period. Informed consent was obtained after the Institutional Review Board-approved protocol was discussed with the patient and/or a parent/legal guardian.

Data were expressed as mean  $\pm$  standard error of the mean (SEM). Statistical analyses were carried out using paired T tests for normally distributed data or the Wilcoxon rank sum test for non-normally distributed data. Results from the same subjects were compared before and after treatment. A  $p$  value  $< 0.05$  was considered significant.

### 3 Results

In total, 16 children met all eligibility criteria. Four were withdrawn because of religious dietary restrictions, as the pancreatic enzyme supplement is of porcine origin. One other patient was non-compliant, leaving 11 patients (eight males, three females) who completed the study protocol.

Pancreatic enzyme supplementation significantly decreased the severity of AD, as measured by the SCORAD index ( $52.3 \pm 5.5$  vs.  $34.6 \pm 7.6$ , respectively;  $p = 0.0008$ ). Clinical improvements were observed in 9 of 11 cases (Fig. 1). An intent-to-treat analysis including the non-compliant case yielded a success rate of 75% (9/12).

As shown in Fig. 2, pretreatment intestinal permeability was significantly greater in patients with AD than in

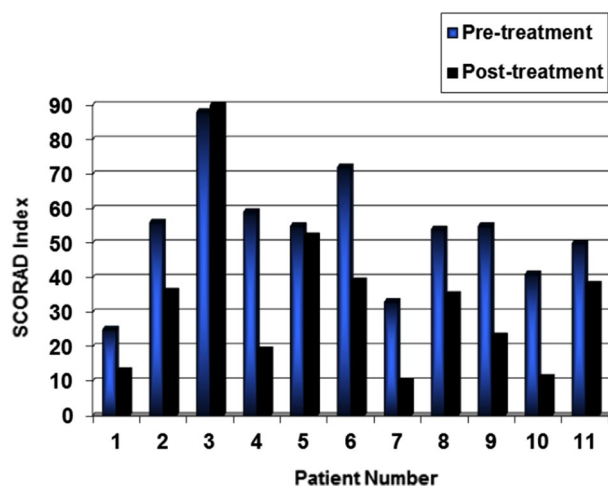


**Fig. 1** Pancreatic enzyme supplementation (6 weeks) significantly improved the severity of atopic dermatitis in a cohort of pediatric patients with multiple food allergies. A significant improvement in Scoring Atopic Dermatitis (SCORAD) index scores was seen in 9 of 11 cases. Mean  $\pm$  standard error scores before and after treatment were  $52.3 \pm 5.5$  vs.  $34.6 \pm 7.6$ , respectively ( $p = 0.0008$ )

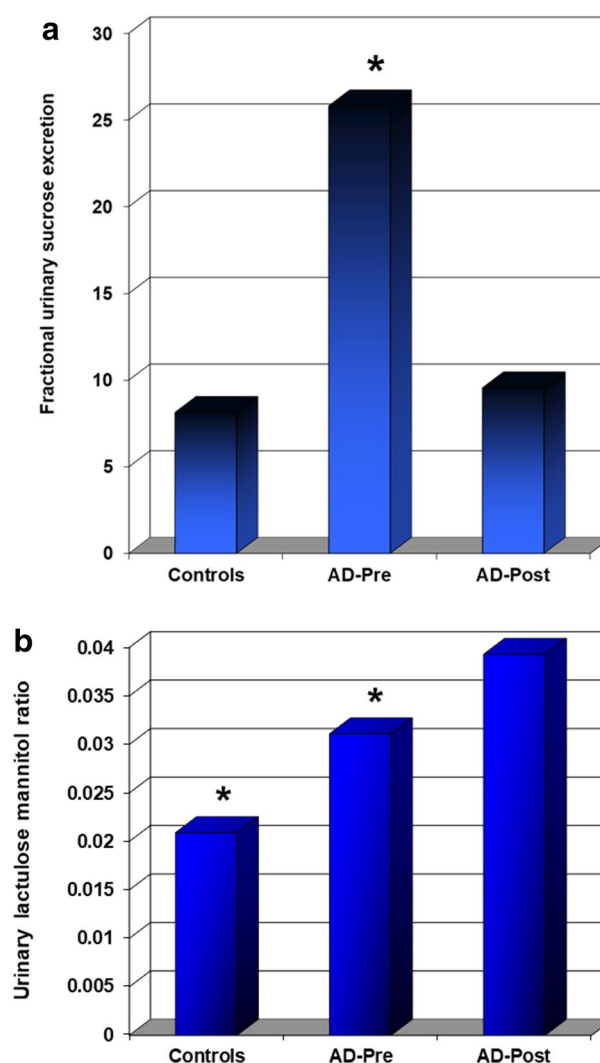


**Fig. 2** Intestinal permeability tests in a cohort of children with severe atopic dermatitis and multiple food allergies. **a** Sucrose excretion rates. The vertical axis shows the mass of sucrose collected in the overnight urine specimen after the oral load ( $g \times 1/1000$ ). The fractional urinary excretion of sucrose (mean  $\pm$  standard error), a marker of gastroduodenal permeability, was significantly greater among children with atopic dermatitis and multiple food allergies (AD-Pre,  $n = 11$ ) than in age-matched healthy controls ( $n = 8$ );  $26.5 \pm 5.0$  and  $7.7 \pm 1.4$  (\* $p < 0.05$  by Wilcoxon rank sum test). After treatment with pancreatic enzyme supplements for 6 weeks (AD-Post), the fractional urinary sucrose excretion improved to  $9.7 \pm 1.5$ , similar to that in controls). **b** Small bowel permeability, as measured by urinary lactulose:mannitol ratio (normal  $< 0.025$ ), was significantly greater among children with atopic dermatitis and multiple food allergies (AD-Pre) than among controls ( $0.032 \pm 0.01$  vs.  $0.021 \pm 0.005$ ; \* $p = 0.01$  by Wilcoxon rank sum test). No significant change was seen after treatment with pancreatic enzyme supplements (AD-Post  $0.0039 \pm 0.01$ ;  $p$  value not significant vs. AD-Pre)

controls. Gastroduodenal permeability, as measured by urinary fractional sucrose excretion, approached normal values after treatment in the AD group (Fig. 2a). No improvement in sucrose excretion was observed in the two nonresponders.

No improvement in the urinary lactulose:mannitol ratio was observed with treatment (Fig. 2b). Pancreatic enzyme supplementation was well tolerated in all cases, without adverse events.

## 4 Discussion

In this proof-of-principal pilot study, intestinal barrier function was observed to be abnormal in children with severe AD and multiple food allergies, supporting the hyperpermeable gut as a contributing factor. Pancreatic enzyme supplementation resulted in significant, objective clinical improvement of dermatitis in 9 of 11 cases (81.8%). However, considering the one non-compliant patient, the response rate was 75% (9 of 12) on an intent to treat basis. Follow up visits at 3–4 months after pancreatic enzyme supplements were initiated were available in 7 of 9 responders. Improvement in the dermatitis was sustained in all 7 cases (data not shown). Our data suggest that enzymatic degradation of dietary proteins resulted in decreased allergen uptake, improving AD. Although we did not investigate pancreatic function, it seems unlikely that exocrine pancreatic function was abnormal in the absence of symptoms of malabsorption. A study in adult AD failed to show evidence for pancreatic proteolytic maldigestion as a pathogenetic factor [40]. Pancreatic function and gut barrier integrity are known to mature during early infancy [41, 42].

Pancreatic enzyme supplementation was associated with improved gastroduodenal permeability. However, the urinary lactulose:mannitol ratio did not improve. Excessive antigen uptake across the intestine has been demonstrated in pediatric patients with atopic eczema employing Ussing chambers to measure horseradish peroxidase transport in vitro [30]. Excessive permeability may initiate and perpetuate host immune responses to common but unidentified intraluminal antigens, including foods. We believe that the pancreatic enzyme supplementation could hydrolyze these antigens, removing the antigenic stimulus.

Limitations of our study include the open-label design and the small study size. The study group also covered a broad age range of pediatric patients, from infancy through adolescence. This pilot study did not test different doses of pancreatic enzyme supplementation or treatment durations, nor were long-term outcomes tracked for more than 3 months.

## 5 Conclusions

This is the first study supporting the utility of pancreatic enzyme supplementation in patients with severe AD and multiple food allergies. Our data suggest that AD is

associated with excessive intestinal permeability and that gastroduodenal permeability improved with the enzyme treatment. Based on these pilot results, further studies, including varying doses and duration of enzyme therapy using a double-blind placebo-controlled design, are warranted.

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## Compliance with Ethical Standards

**Ethical approval** The study design and consent forms were approved by the research institution's investigational review board, and the study was performed in accordance with the ethical standards of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study or their legal guardians.

**Authorship statement** Sanford Singer, Jonathan Meddings, Julie Powell, Anne Desroches, Ernest G. Seidman participated in the design and implementation of the study, data collection and interpretation, and manuscript preparation. Jamie Koenekoop participated in updating, revising, and preparing the manuscript. All authors approved the final version of the article.

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**Conflict of interest** S. Singer, J. Koenekoop, J. Meddings, J. Powell, A. Desroches, and E.G. Seidman have no conflicts of interest relevant to the contents of this manuscript.

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