

Induction of atopic dermatitis by inhalation of house dust mite

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Background: The pathogenetic role of house dust mite in atopic dermatitis remains controversial. Recent studies have shown that intensive epicutaneous contact of house dust mite allergen with premanipulated skin may induce dermatitis. It is, however, uncertain whether such conditions are met during natural contact with house dust mite. In the past, allergen inhalation has been suggested to induce exacerbation of atopic dermatitis. The aim of this study was to investigate whether dermatitis could be induced in patients with atopic dermatitis by inhalation of house dust mite.

Methods: Twenty patients with atopic dermatitis underwent bronchial provocations with house dust mite. Challenge tests were performed with four concentrations of a standardized house dust mite extract in a double-blind, randomized, placebo-controlled fashion. Spirometry was performed, and FEV₁ was measured before and after each challenge dose. Changes in severity or localization of itching or erythema were recorded.

Results: In nine of 20 patients with atopic dermatitis bronchial challenge with house dust mite induced unequivocal skin symptoms after 1.5 to 17 hours. Pruritic erythematous lesions on noninvolved sites together with exacerbations of existing lesions were seen in three patients. Three patients had an exacerbation only, and three other patients had new lesions only. In eight of nine patients with house dust mite inhalation-induced dermatitis, skin symptoms were preceded by an early bronchial reaction. All patients with house dust mite-induced dermatitis had a history of asthma, and as a group they had a higher mean blood total IgE level compared with the "negative skin responders." One patient had pruritic erythema on the placebo challenge day, without a preceding bronchoconstrictive reaction. The number of patients who had a skin response on the house dust mite challenge day was significantly higher than the number of patients who had a skin response on the placebo day ($p = 0.011$ [Prescott's test]).

Conclusions: The respiratory route may be relevant in the induction and exacerbation of dermatitis in a subset of patients with atopic dermatitis who have early bronchial reactions after house dust mite inhalation, a history of asthma, and an elevated blood total IgE level. Furthermore, these findings suggest a possible causal relationship between bronchial reactions and skin reactions. (*J Allergy Clin Immunol* 1996;97:1064-70.)

Key words: Atopic dermatitis, house dust mite, bronchial challenge, early bronchial reaction, total IgE

Atopic dermatitis (AD) is a pruritic relapsing chronic skin disease, associated with positive immediate-type intracutaneous test responses to inhalant allergens, particularly house dust mite (HDM).¹ In the majority of patients with AD

Abbreviations used

AD:	Atopic dermatitis
HDM:	House dust mite
DFEV ₁ :	FEV ₁ after HDM challenge (% baseline) – FEV ₁ after diluent challenge (% baseline)

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increased serum levels of HDM-specific IgE can be demonstrated.² However, the pathogenetic role of HDM in AD remains controversial. Evidence favoring a role for HDM includes uncontrolled

TABLE I. Characteristics of patients with AD involved in the study

Patient No.	Age (yr)	Gender	DSS		History of Asthma Attacks	FEV ₁ (% predicted)		EO ($\times 10^6/L$)	IgE (U/ml)	HDM-specific IgE (PRU/ml)*
			Day p	Day h		Day p	Day h			
1	28	F	15	15	+	99	99	120	3610	184
2	27	F	9	9	—	88	90	90	41	1.6
3	25	M	17	16	+	108	108	400	1371	26
4	23	M	10	10	—	95	93	470	1693	50
5	26	F	0	0	—	107	105	70	241	0
6	28	F	5	5	+	108	105	270	544	26
7	25	M	20	17	+	71	68	700	14810	796
8	24	M	26	27	+	102	85	730	19410	917
9	24	F	11	9	+	71	61	810	1750	70
10	20	F	13	13	+	81	81	270	152	14.3
11	28	F	25	25	+	96	89	960	9960	37.7
12	30	M	15	17	+	97	95	280	862	270
13	29	M	13	21	+	102	103	940	14000	823
14	26	F	9	9	+	111	109	650	467	98
15	66	M	35	35	—	131	137	230	6880	358
16	28	M	20	21	+	98	98	910	17700	46
17	24	M	21	23	+	95	95	230	17750	752
18	18	F	8	8	+	96	92	340	1979	391
19	19	F	0	0	—	103	99	210	73	0.4
20	28	M	9	8	+	98	94	420	902	15.6

DSS, Baseline dermatitis severity score based on the quick scoring system of Costa et al. (<15, mild dermatitis; 15-30, moderate dermatitis; >30, severe dermatitis); Day p, day of placebo challenge; Day h, day of house dust mite challenge; EO, eosinophil count; PRU, Pharmacia RAST units.

*Determined with CAP RAST (Pharmacia, Uppsala, Sweden).

studies in which improvement in AD occurred after careful HDM avoidance³ or use of bed covers.⁴ The mechanism of penetration of HDM allergen is not clear yet. Theoretically, there are two possible routes: (1) directly through the epidermis and (2) by inhalation.

In the last decade, attention has been focused on the epidermal route. Occlusive testing with HDM allergen elicited an eczematous reaction only on abraded,⁵ scratched,⁶ sodium lauryl sulfate-irritated,⁷ or eczematous⁸ skin. Sporadically, positive patch test reactions were noticed on uninvolved skin that was not manipulated.^{9,10} Testing on manipulated skin was justified by assuming that these manipulations simulate naturally occurring conditions in AD.⁷ It is therefore possible to imagine that worsening of existing dermatitis can be caused by penetration of HDM through damaged stratum corneum. In contrast, penetration of HDM through an intact stratum corneum in AD is hard to imagine, which makes the relevance of the epidermal route in the induction of new lesions doubtful. The main HDM antigens are glycoproteins occurring in mite feces (Der p 1; molecular weight, 24,000 d) or bodies (Der p 2; molecular

weight, 15,000 d) of *Dermatophyoides pteronyssinus*.¹¹ The feces are 10 to 40 μ m in diameter and are easily respirable.¹¹

Early studies support the significance of HDM, inhalation, which was seen to induce an exacerbation of preexisting eczematous lesions.¹²⁻¹⁴ Likewise, inhalation of other inhalant allergens, such as mold^{12,13} and pollens of birch,¹³ grass,¹⁴ and ragweed¹⁵ caused exacerbation of AD. Occurrence of new skin lesions after inhalation of allergens was only occasionally reported.^{14,16} The time interval between inhalation and skin symptoms was stated by most authors to be "some hours." A few authors mentioned rhinorrhea^{12,13} or bronchoconstriction¹⁴ preceding the skin symptoms in some patients. These early studies were relatively small and poorly controlled, and an open study design was used.

The aim of this study was to determine whether we could induce an exacerbation of existing dermatitis or new dermatitis lesions in patients with AD by means of double-blind, randomized, placebo-controlled bronchial provocations with HDM extract. An additional aim was to determine whether this dermatitis reaction is associated with bronchial symptoms.

TABLE II. Respiratory and cutaneous symptoms during HDM and placebo challenge tests in patients with AD

Patient No.	Day	Highest HDM concentration (BU/ml)	FEV ₁ -fall (min)	Respiratory symptoms (min)	Cutaneous symptoms (min)
1	p		3% (30)		New itchy erythema in right elbow fold (210), lasting 4 hr
	h	10,000	3% (30)		
2	p	—	3% (30)		
	h	10,000	2% (20)		
3	p	—	2% (20)		
	h	10,000	20% (40)	Dyspnea (40)	New itchy erythema on dorsal aspect of hands (240), lasting 6 hr
4	p	—	0% (20)		
	h	10,000	15% (20)	Dyspnea (20)	
5	p	—	0 (20)		
	h	10,000	3% (20)		
6	p	—	6% (20)		
	h	10,000	12% (20)		New itchy erythema on neck (360), lasting 2 days
7	p	—	4% (20)		
	h	2,000	19% (20)	Dyspnea (5)	Generalized exacerbation of existing lesions (16 hr)
			18% (7-26 hr)	Dyspnea (6-28 hr)	Itchy erythema on new sites (24 hr), lasting 3 days
8	p	—	0 (20)		
	h	2,000	21% (20)	Dyspnea (5)	Exacerbation of existing lesions on forehead (300), new itchy erythema on upper chest, lasting 6 hr
9	p	—	—7%		
	h	10,000	29% (20)	Dyspnea (15)	New itchy erythema on left forearm (90), lasting 1 day
10	p	—	9.3% (0)		
	h	400	17% (20)	Dyspnea (15)	
11	p	—	23% (20)	Dyspnea (10)	
	h	10,000	27% (30)	Dyspnea (15)	Exacerbation of existing lesions in left elbow fold (90), lasting 8 hr
12	p	—	3% (20)		
	h	2,000	22.5% (20)	Dyspnea (5)	New itchy erythema on both upper arms, exacerbation of existing lesions on left forearm (360), both shoulders, and face (600), lasting 5 days
13	p	—	8% (40)		
	h	2,000	40% (30)	Dyspnea (20)	
			40% (7 hr)	Dyspnea (6 hr)	Exacerbation of existing lesions periorally, left side neck (420), lasting 3 days
14	p	—	0%		
	h	400	14% (20)	Dyspnea (10)	
			43% (7.5 hr)	Dyspnea (7 hr)	
15	p	—	4% (0)		
	h	10,000	10% (40)		
16	p	—	2% (20)		
	h	2,000	24% (20)	Dyspnea (8)	
17	p	—	3% (20)		
	h	400	17% (40)	Dyspnea (20)	
			15.5% (11 hr)	Dyspnea (9 hr)	Exacerbation of existing lesions on upper arms, buttocks, knee folds (17 hr), lasting 2 days

Time elapsed since last provocation is given in minutes, unless otherwise stated.

p, Placebo challenge day; h, HDM challenge day; FEV₁-fall, percentage of FEV₁ decrease from preprovocation value to lowest postprovocation value.

TABLE II. Cont'd

Patient No.	Day	Highest HDM concentration (BU/ml)	FEV ₁ -fall (min)	Respiratory symptoms (min)	Cutaneous symptoms (min)
18	p	—	2% (0)		
	h	400	48% (20)	Dyspnea (10)	
			18% (6 hr)	Dyspnea (6 hr)	
19	p	—	8% (20)		
	h	10,000	10% (0)		
20	p	—	2% (20)		
	h	10,000	32% (20)	Dyspnea (10)	

METHODS

Twenty patients with AD and positive intracutaneous test responses to HDM were selected. All medication was stopped according to the following washout schedule: topical or inhaled steroids and disodium cromoglycate, 2 weeks; antihistamines, 1 week; inhaled salbutamol or ipratropium, 1 day. No patient had been treated with systemic corticosteroids, cyclosporine, or ultraviolet light in the preceding 6 months. The challenge tests were performed in a double-blind, randomized, placebo-controlled fashion. A technician not directly involved in the study used a randomization scheme to determine the sequence of challenges so that patients and investigators were unaware of the nature of the challenge. After the last challenge was performed and the response scored, the code was broken.

The active test solution consisted of four concentrations (80, 400, 2000, 10,000 BU/ml) of standardized HDM (*D. pteronyssinus*, SQ 503; ALK Benelux, Groningen, The Netherlands) diluted in phosphate buffer containing 0.5% phenol and 0.03% human serum albumin. Increasing concentrations were inhaled during 1 minute at intervals of 20 minutes. Spirometry was performed with a rolling seal dry spirometer (Morgan 130; Morgan Ltd., Rainham, Gillingham, U.K.) fitted to a two-way valve box. This was connected to a De Vilbiss 464 nebulizer (De Vilbiss Medizinische GmbH, Langen, Germany) with an output of 0.13 ml/min. Forced expiratory volume in 1 second (FEV₁) was measured immediately before and immediately after each challenge dose, according to the method described by Weersink et al.¹⁷ The inhalation was stopped as soon as the fall in FEV₁ was 15% or more of baseline FEV₁ (early bronchial reaction). During the first hour after the last challenge, FEV₁ was measured every 10 minutes. After the first hour, it was measured every hour for 6 hours. The late bronchial reaction was defined as a decrease of 15% or more in the baseline FEV₁, 4 to 7 hours after the challenge. Before the first challenge, severity of dermatitis was scored, based on the quick scoring system proposed by Costa et al.¹⁸ Severity of itching was graded from 1 to 4 (mild to unbearable). Patients were requested to mention changes in severity of itching or occurrence at a previously uninvolved site. In these cases

the skin was evaluated for the presence of erythema. Changes in severity or localization of itching or erythema were recorded. Skin symptoms were considered significant when there was an exacerbation of existing eczematous lesions (i.e., more pronounced erythema and/or more extensive area involved, together with severe itching [itching score, 3+ or 4+]), or when new severely itching erythematous lesions developed. The diluent (placebo) solution consisted of the phosphate buffer, which was inhaled four times. The diluent challenge procedure and evaluation of bronchial and skin symptoms were exactly the same as those described for the active suspension. The time interval between allergen and placebo challenges was 1 week.

All FEV₁ values were expressed as percentage change from the baseline FEV₁ value, which was measured at the start of every study day. The FEV₁ values were corrected for diurnal variation by use of the following formula at each time point for each patient: DFEV₁ (% baseline) = FEV₁ after HDM challenge (% baseline) – FEV₁ after diluent challenge (% baseline). The number of skin responders on the HDM challenge day was compared with the number of skin responders on the placebo challenge day by means of the test described by Prescott.¹⁹ Mean values of dermatitis severity score before provocation, FEV₁ before and after provocation, log₁₀-transformed values of blood eosinophils, total IgE, and HDM-specific IgE in "positive and negative skin responders" were compared by means of Student's *t* test for unpaired data. Differences were considered to be significant at a *p* value of less than or equal to 0.05.

RESULTS

Table I summarizes clinical and laboratory characteristics of the patients with AD. In nine of 20 patients unequivocal skin symptoms could be induced by bronchial inhalation of HDM (Table II). Three patients had new severely itching erythematous lesions together with exacerbations of existing lesions, three patients had exacerbation of existing lesions only, and three other patients had new lesions only. In seven patients skin symptoms occurred after 1.5 to 7 hours and lasted for 6 hours

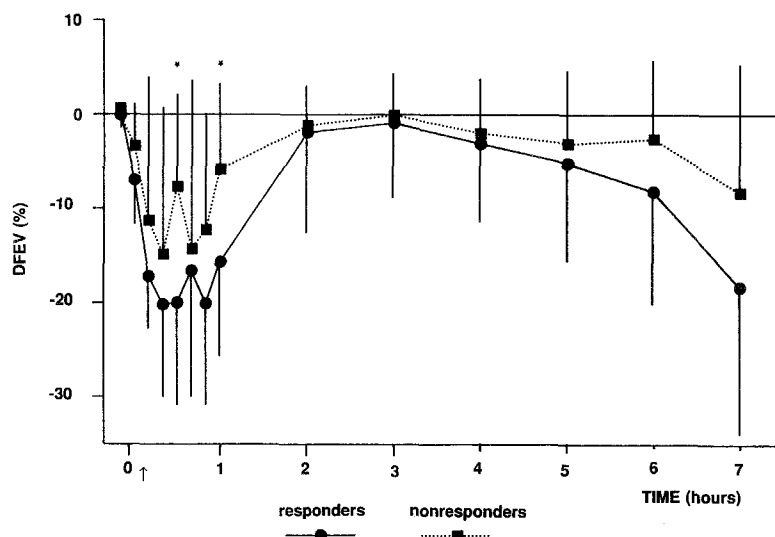


FIG. 1. Time course of DFEV₁ in positive skin responders and negative skin responders. Values indicated are means $\pm 0.5 \times$ SD. $\uparrow$ Directly after inhalation. *Significant difference.

to 5 days. Two patients (nos. 7 and 17) had an exacerbation of AD after 16 to 17 hours, which lasted for 2 to 3 days. The number of patients who had a skin response on the HDM challenge day (nine) was significantly higher than the number of patients who had a skin response on the diluent day (one) ($p = 0.011$). No urticarial reactions were observed.

All nine patients with allergen inhalation-induced dermatitis also had a history of asthma. In these patients skin symptoms were preceded by a fall in FEV₁ (12% to 40%) during the early phase (<1 hour) (Fig. 1). In eight patients this fall in FEV₁ exceeded 15% (early bronchial reaction) and was accompanied by dyspnea. In three of these patients a late bronchial reaction was also observed. In the patient who had itchy erythema on the diluent challenge day, no preceding FEV₁ decrease occurred. Four patients had an early bronchial reaction after HDM challenge without subsequent skin lesions (Fig. 1). One of these patients also had a late bronchial reaction. Mean values for DFEV₁ were significantly lower in the "positive skin responders" compared with the "negative skin responders," 30 and 60 minutes after HDM provocation (Fig. 1).

Mean values for dermatitis severity score before provocation, log-eosinophils, and log-HDM-IgE tended to be higher in positive skin responders compared with negative skin responders (Table III). Statistical significance was reached only for log-total IgE, which was higher in positive skin responders.

DISCUSSION

We have demonstrated that nine of 20 patients with AD had an exacerbation of preexisting lesions, new lesions, or both after double-blind, placebo-controlled bronchial provocation with HDM. Our findings confirm results of older, open studies on HDM inhalation.¹²⁻¹⁴ The time of onset of skin symptoms in our study varied between 1.5 and 17 hours, which corresponds with the findings of Storck (0.5 to 24 hours).¹⁴

In five patients, a sustained exacerbation of AD was induced, whereas in the other patients, the skin reactions had a transient nature. More sustained reactions may have resulted if the provocation had been repeated. Repeated inhalation challenges by Tuft et al.¹² resulted in progressive worsening of dermatitis. Repeated challenges probably better reflect natural exposure than a single allergen challenge.

Eight of nine patients with AD who had a dermatitis reaction after HDM inhalation had a preceding early bronchial reaction, and all positive skin responders had a history of asthma. In an early study initial bronchoconstrictive response was noticed in all patients with AD who experienced skin symptoms after bronchial provocation, despite the absence, in these patients, of a history of asthma.¹⁴ In our patient group one case of dermatitis was observed after diluent challenge. This reaction was considered a naturally occurring relapse and was not preceded by bronchoconstriction.

In five patients no bronchial reactions could be detected after HDM challenge, possibly because

TABLE III. Mean values of characteristics in patients with a cutaneous reaction (positive responders) and without a cutaneous reaction (negative responders) after HDM inhalation

	Positive responders		Negative responders		<i>P</i> Value*
	Mean	SD	Mean	SD	
DSS	18	7	12	10	0.136
FEV ₁	90	16	100	15	0.179
log-EO	2.7	0.3	2.3	0.6	0.078
log-total IgE	3.7	0.5	2.8	0.9	0.020
log-HDM-IgE	2.3	0.7	1.7	0.7	0.125

EO, Eosinophils.

*Student's *t* test.

their respiratory tracts were unresponsive. Four of these patients did not have asthma, and in one patient (no. 1) asthma was very mild and did not require drug treatment.

The pathophysiologic mechanism of the development of dermatitis after bronchial provocation has not been elucidated. An HDM-specific IgE-related reaction seems likely. The following hypotheses may be put forward.

Skin allergen interaction theory

Dermatitis may develop when allergens cross the respiratory barrier, enter the circulation, and are distributed (free or complexed with antibodies) to the skin.²⁰ In the skin, the allergen (or allergen-antibody complex) may interact with several cell types bearing IgE molecules or IgE receptors: mast cells, HDM-specific T helper cells, antigen-presenting cells, or eosinophilic granulocytes.

Allergens induce mast cell release of various vasoactive mediators and mediators that are chemotactic toward eosinophilic granulocytes.²¹

After in vitro HDM challenge, HDM-specific T-cell clones produced large quantities of IL-4, which enhanced expression of the low-affinity Fc receptor for IgE (CD23) on antigen-presenting cells.²²

In vitro observations support the concept of facilitated presentation of complexed antigen on CD23⁺ antigen-presenting cells.²³ As a result of this facilitated antigen presentation, a 1000-fold lower Der p 2 concentration was required for T-cell activation, leading to secretion of IL-4.²³ High-affinity Fc receptor-bound IgE⁺ Langerhans' and allergen-specific T_{H2} cells were both present in clinically noninvolved skin in a subgroup of patients with AD who had a positive allergen patch test response.²⁴ In our study all patients with HDM-induced dermatitis had an elevated HDM-specific IgE level. Therefore it may be hypothe-

sized that minute amounts of HDM antigens bind with HDM-specific IgE⁺ Langerhans' cells, which interact with HDM-specific T cells, leading to activation of T cells.

Eosinophilic granulocytes are believed to play an important role in AD²⁵ and can be directly triggered by interaction of complexed allergen with the low-affinity IgE receptor.²⁶

Bronchial allergen interaction theory

Dermatitis may develop after bronchial provocation as a result of local stimulation of bronchial associated immune system, with subsequent release of inflammatory mediators and cytokines in the circulation. There is indirect evidence for the presence of increased blood levels of cytokines involved in activation of eosinophils in asthmatic patients.²⁷ Bronchial biopsy specimens obtained after allergen inhalation revealed increased numbers of eosinophils and cells expressing messenger RNA for IL-4, IL-5, and granulocyte-macrophage colony-stimulating factor-1.²⁸

Neuro-immune theory

Dermatitis after bronchial provocation may be caused by local stimulation of specific IgE-bearing mast cells in the respiratory mucosa, which activate neurohumoral pathways, finally stimulating the release of neuropeptides, which can trigger inflammatory cascades.²⁹ This hypothesis may be supported by the findings of Tuft et al.,³⁰ who reported exacerbation of affected areas after allergen inhalation, preceded by local sweating. Both the sweating response and the exacerbation could be prevented by prior injection of an antihistamine.³⁰

In conclusion, we have demonstrated that induction of dermatitis in patients with AD by means of double-blind, randomized, placebo-controlled bronchial provocation with HDM may occur. The respiratory route is probably relevant for the in-

duction of dermatitis in a subset of patients with AD who have an early bronchial reaction after HDM inhalation, a history of asthma, and an elevated total IgE level.

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