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Increase in vesicular hand eczema after house dust mite inhalation provocation: a double-blind, placebo-controlled, cross-over study

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Summary

Background. It is unclear whether the respiratory tract is involved in eliciting or aggravating eczematous lesions in patients with vesicular hand eczema.

Objectives. To investigate the effect of inhalation of house dust mite (HDM) on vesicular hand eczema.

Methods. Eighteen patients with vesicular hand eczema and HDM allergy received inhalation challenges with four concentrations of HDM in a randomized, double-blind, placebo-controlled, cross-over study. Early asthmatic reactions and late asthmatic reactions were defined as a placebo-corrected fall of 15% or more from baseline of forced expiratory volume in 1 second. Hand eczema was scored according to the Dyshidrotic Eczema Area and Severity Index (DASI) at baseline, and 1, 6, 24 and 48 hr.

Results. The median DASI increased significantly as compared with baseline at 6 and 48 hr after HDM inhalation. This increase was significantly different between the provocations at 6 hr. The median vesicles score increased significantly from baseline at 24 and 48 hr. Patients with a placebo-corrected increase in the number of vesicles at 24 hr and 48 hr had significantly more often late asthmatic reactions than those without an increase in the number of vesicles. Patients with a placebo-corrected increase of the DASI score at 24 hours had as a group a higher mean total IgE level than those without an increase of the DASI score.

Conclusion. Hand eczema increased significantly more after HDM provocation than after placebo provocation. An increase in the number of vesicles was preceded by late asthmatic reactions. The group patients with an increase of hand eczema tended to have a higher mean total IgE level.

Key words: allergens; bronchial provocation tests; *Dermatophagoides pteronysinnus*; dyshidrotic eczema.

Hand eczema is not a homogeneous disease entity. It is associated with many different aetiologies and morphologies. External and predisposing endogenous factors play a role in hand eczema. Being atopic is assumed to be related to the risk of developing and maintaining hand eczema. Vesicular hand eczema (dyshidrotic eczema or pompholyx) is, by definition, the development of isolated vesicles on the palms, the palmar aspects of the fingers, and the sides of the fingers. The condition is eruptive, and is accompanied by inflammatory erythema of variable intensity and severe pruritus. The cause may be exposure to allergens or irritants, or unknown. The degree of association between vesicular hand eczema

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and atopy is unclear. In 1992, Lodi et al. (1) reported atopy to be a predisposing factor in the pathogenesis of vesicular hand eczema. In 2003, Bryld et al. (2) reported no association of vesicular hand eczema and atopic dermatitis or atopy, defined as a history or the presence of asthma, hay fever, flexural eczema, or childhood eczema.

The pathogenic role of house dust mite (HDM) in atopic dermatitis remains unclear, and ambiguous findings have been reported. Studies on HDM in impermeable mattress casings showed some effect (3, 4) or no effect (5, 6). The respiratory route may be relevant in the exacerbation of atopic dermatitis. In 1996, Tupker et al. (7) reported that inhalation of HDM aggravated dermatitis in patients with atopic dermatitis who had early asthmatic reactions (EARs). Brinkman et al. (8) reported in 1997 that allergen inhalation challenge caused a flare-up of skin lesions in atopic dermatitis patients, and that it was more prominent in atopic dermatitis patients who already had IgE-mediated allergic inflammation in the lung.

On the basis of present knowledge, we assumed that a significant proportion of patients with vesicular hand eczema are allergic to HDM. Therefore, we hypothesized that the respiratory tract could be involved in eliciting or aggravating eczematous lesions. The aim of this study was to investigate the effect of inhalation provocation with HDM on vesicular hand eczema in atopic individuals. Further insights may be helpful in guiding future management and improvement in the prevention of flares in susceptible individuals.

Methods

Study design

This was a randomized, double-blind, placebo-controlled, cross-over study.

Setting and study period

The study site was the dermatology outpatient clinic and the department of Allergy of the University Medical Center in Groningen, The Netherlands. Data were collected between 2003 and 2010.

Inclusion and exclusion criteria

Eligible patients were aged 18–70 years with a morphological diagnosis of vesicular hand eczema (9). We included patients who had mild to moderate vesicular hand eczema, disease severity of 0–60 according to the Dyshidrotic Eczema Area and Severity Index (DASI) (10), and a positive prick test reaction to *Dermatophagoides pteronyssinus* (SQ 503, 10 000 BU/ml; ALK Benelux, Lelystad, The Netherlands). A positive prick test reaction was defined as a histamine equivalent prick of ≥ 0.5.

Exclusion criteria were severe asthma, a forced expiratory volume in 1 second (FEV_1) $< 80\%$ of the predicted value, and pregnancy. Other exclusion criteria were phototherapy, systemic corticosteroids, inhaled corticosteroids, nedocromil, disodium cromoglycate or other systemic immunomodulating drugs within the past 4 weeks, antihistamines and β-blocking drugs in the previous 7 days, long-acting $\beta 2$-sympathomimetics in the previous 48 hr, and short-acting $\beta 2$-sympathomimetics in the previous 12 hr.

Procedure

Patients who were referred for vesicular hand eczema and who had been treated for vesicular hand eczema in recent years at the department of Dermatology were asked to participate. A request for participation in the study was also made in a local newspaper. Patients were informed of the study by an independent physician. If they were interested in participating, they received an appointment for screening on eligibility by the investigator. The patients were tested for type 1 allergy by prick testing with HDM allergen (*D. pteronyssinus*). Examination for pulmonary pathology was followed by measurement of spirometry (vital capacity and FEV_1). Fungal infections on the hands and feet were ruled out. When patients fulfilled the inclusion criteria, they were included in the study. A history of asthma was defined as present if patients reported a diagnosis of asthma by a physician. A history of atopic dermatitis was defined as present if patients reported a diagnosis of atopic dermatitis confirmed by a physician. Current atopic dermatitis was defined according to the UK working party criteria (11). If patients used topical steroids or other anti-inflammatory topical medications, they had to continue it at the same frequency and strength during the study.

Randomization and blinding

A laboratory technician not directly involved in the study used a computer-generated randomization scheme to determine the sequence of challenges, so that the patients and the investigators were unaware of the nature of the challenge. The outcome assessor trained in scoring hand eczema severity was blinded. The code was broken after the last challenge had been performed and the response had been scored.

Ethics committee

The protocol was approved by the local research ethics committee, and written informed consent was obtained from all of the participants.

Inhalation provocation

The active test solution consisted of four concentrations (80, 400, 2000 and 10 000 BU/ml) of standardized HDM (*D. pteronyssinus*, SQ 503; ALK Benelux) diluted in phosphate buffer containing 0.5% phenol and 0.03% human serum albumin. The placebo test solution consisted of the phosphate buffer containing 0.5% phenol and 0.03% human serum albumin. Challenges always started between 8.30 and 9.00 in the morning. Increasing concentrations were inhaled for 1 min at intervals of 15 min. In patients 1–6, spirometry was performed with a rolling seal dry spirometer (Morgan 130; Morgan Ltd, Rainham, Gillingham, UK) 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. Patients 7–18 were tested with the Masterlab Trans spirometer (Spirometer Erich Jaeger AG, Würzburg, Germany). All equipment was calibrated weekly.

An EAR and a late asthmatic reaction (LAR) may occur after exposure to an allergen. FEV_1 was measured at different times in order to assess EARs and LARs (12). FEV_1 was measured immediately before and immediately after each challenge dose. After the last challenge, FEV_1 was measured after 15, 20, 30, 40, 50 and 60 min. Thereafter, FEV_1 was measured hourly in a standard manner from 11.00 to 17.00.

The inhalation was stopped as soon as the fall in FEV_1 from baseline was $\geq 15\%$. In that case, the following schedule was used: FEV_1 was measured after 15, 20, 30, 40, 50 and 60 min. The placebo challenge procedure was the same as described for the active suspension. The time interval between HDM and placebo challenges was 2–4 weeks.

If an EAR occurred and the FEV_1 decreased from baseline by $> 35\%$, the patients received two doses of 200 μg of salbutamol by inhalation. In cases of LAR, the patients were prescribed 200 μg of salbutamol and 400 μg of budesonide. The dose was determined by the amount of the fall in FEV_1.

Assessments

Hand eczema

Hand eczema was scored with the DASI before the first challenge and 1, 6, 24 and 48 hr after the first challenge on the HDM day and on the placebo provocation day (10). This index combines intensity items (vesicles, erythema, and desquamation) with the subjective item (itch), and with the extent of the affected area. Vesicles was scored as the estimation of the total number of vesicles divided by the total size of the affected area in square centimetres (0 points, absent; 1 point, >0 to < 2 vesicles/cm^2; 2 points, 2–8 vesicles/cm^2; 3 points, > 8 vesicles/cm^2). Erythema, desquamation and itch were scored from 0 to 3 for each item (0 points, absent; 1 point, mild; 2 points, moderate; 3 points, severe). Grading of the items erythema, desquamation and itch was representative for all of the affected areas. The affected area was scored on the basis of the mean percentage of affected skin of the total palm (0 points, absent; 1 point, 1–20%; 2 points, 21–40%; 3 points, 41–60%; 4 points, 61–80%; 5 points, 81–100%). The total score results from the sum of the four intensity/subjective items (vesicles, erythema, desquamation, and itch) were multiplied by the affected area score points to provide a score ranging from 0 to 60 for one hand. The sum of the right hand and the left hand provided the DASI score, which ranged from 0 to 120, with the higher scores representing more severe eczema. The DASI sub-scores of the items vesicles, erythema, desquamation and itch were each scored from 0 to 3 points. The sum of the sub-scores of the right hand and the left hand was the DASI sub-score, which ranged from 0 to 6 for the items vesicles, erythema, desquamation and itch, and from 0 to 10 for the sub-score affected area. The assessment of hand eczema was carried out by one experienced nurse practitioner.

Spirometry

The fall in the FEV_1 values, represented as ΔFEV_1, was expressed as the percentage change from baseline, which was measured at the start of both provocation days. The maximum ΔFEV_1 values were corrected for diurnal variation, to produce the ΔFEV_1 placebo-corrected in the first hour after the provocation and ΔFEV_1 placebo-corrected 3–8 hr after the provocation, according to the following formula: ΔFEV_1 placebo-corrected (% baseline) = maximum ΔFEV_1 HDM (% baseline) – corresponding ΔFEV_1 placebo (% baseline). The EAR was defined as ΔFEV_1 placebo-corrected (% baseline) $\geq 15\%$ in the first hour after the provocation. The LAR was defined as ΔFEV_1 placebo-corrected (% baseline) $\geq 15\%$ 3–8 hr after the provocation.

Serum IgE levels and eosinophils

Serum eosinophils were measured on both provocation days before the first challenge and 24 hr after the first challenge. Serum concentrations of eosinophils $> 0.4 \times 10^9$/l were considered to be increased.

We evaluated total IgE levels and HDM (*D. pteronyssinus*)-specific IgE levels at the start of every first provocation

day. Serum concentrations of total IgE and HDM-specific IgE were measured with the Radio Allergosorbent Test. Total IgE > 115 kU/l and specific IgE HDM > 0.35 kU/l were considered as positive.

Outcomes

The primary outcome was the between-provocation (HDM versus placebo) differences in ΔDASI at 48 hr. The change in DASI scores and DASI sub-scores at the different time points were corrected for baseline values, represented as ΔDASI and ΔDASI sub-scores.

Secondary outcome parameters included: between-provocation comparison of the ΔDASI scores at 1, 6 and 24 hr; between-provocation comparison of the ΔDASI sub-scores at the different time points; and changes in DASI scores and DASI sub-scores from baseline after HDM and placebo provocation.

We defined HDM responders and placebo responders at different time points as ΔDASI > 0. As there were patients who responded both to HDM and to placebo, we found it necessary to correct the eczema response to HDM for the response to placebo to define skin responders: ΔDASI after HDM > 0 and ΔDASI after HDM > ΔDASI after placebo. We defined sub-score responders as follows: ΔDASI sub-score after HDM > 0 and Δsub-score after HDM > Δsub-score after placebo.

Further secondary outcomes were the differences in: the number of HDM (sub-score) responders and placebo (sub-score) responders; EAR and LAR in skin responders and non-skin responders; EAR and LAR in sub-score responders and non-sub-score responders; correlations between the percentage fall in FEV_1 and skin responders and non-skin responders; and serum IgE levels and blood eosinophils.

Determination of sample size

The sample size was established on the basis of the presumed difference from baseline of DASI 48 hr after the inhalation provocation. In this two-period cross-over study, there are two ΔDASIs per patient. The standard deviation (SD) of these ΔDASIs is estimated to be 28 points. The mean ΔDASI after HDM provocation is compared with the mean ΔDASI after placebo. We expected the DASI to increase by 28 points after HDM provocation and to not increase after placebo provocation. With $\alpha = 0.05$ and $\beta = 0.2$, each group should consist of 18 patients (two-sided two-sample *t*-test).

Statistical analysis

Baseline characteristics are presented as follows: mean (SD) age (years) and n (%) males. For continuous variables, the Kolmogorov–Smirnov test was used to compare the distribution of the patient scores with the standard normal distribution. If the scores fitted the normal distribution, the paired *t*-test was used for *post hoc* comparisons. If scores were not normally distributed, the Wilcoxon test for non-parametric paired data was used for comparisons. Differences in the number of HDM responders and placebo responders were analysed with McNemar's test.

Differences between EAR in skin responders and non-skin responders and LAR in skin responders and non-skin responders were analysed with Fisher's exact test. Logistic regression analysis was used to investigate associations between the percentage fall in FEV_1 and skin responders versus non-skin responders.

Comparisons of IgE levels and eosinophils after HDM provocation in skin responders versus non-skin responders were analysed with an independent samples *t*-test. In the analysis, a serum concentration of total IgE of > 5000 kU/l was considered as 5000 kU/l, HDM-specific IgE > 100 kU/l was considered as 100 kU/l, and HDM-specific IgE < 0.35 kU/l was considered as 0.35 kU/l. PASW™ statistics 18.0 was used for data analyses.

Results

One hundred and forty-nine patients were approached to participate at the department of Dermatology. Recruitment for participation via the newspaper led to a reaction from 34 individuals who were interested in participating in the study. The participant flow throughout the recruitment and inclusion procedure is shown in Fig. 1. A total of 18 patients were randomized to determine the sequence of challenges.

The baseline characteristics of the study population and the baseline serum eosinophils on the HDM challenge day and the placebo challenge day are summarized in Table 1. The mean age was 38 years (SD ± 14 years). Five (28%) males and 13 (72%) females participated in the study.

Hand eczema

As shown in Table 2, significant increases in median DASI score and median DASI sub-scores were seen only after provocation with HDM. After placebo provocation, no significant differences from baseline were seen at any time point.

At 48 hr, a significant increase in median DASI as compared with baseline was seen after HDM provocation ($p = 0.005$), but no significant difference in ΔDASI between HDM and placebo was seen at that time point. A significant increase in median DASI as compared

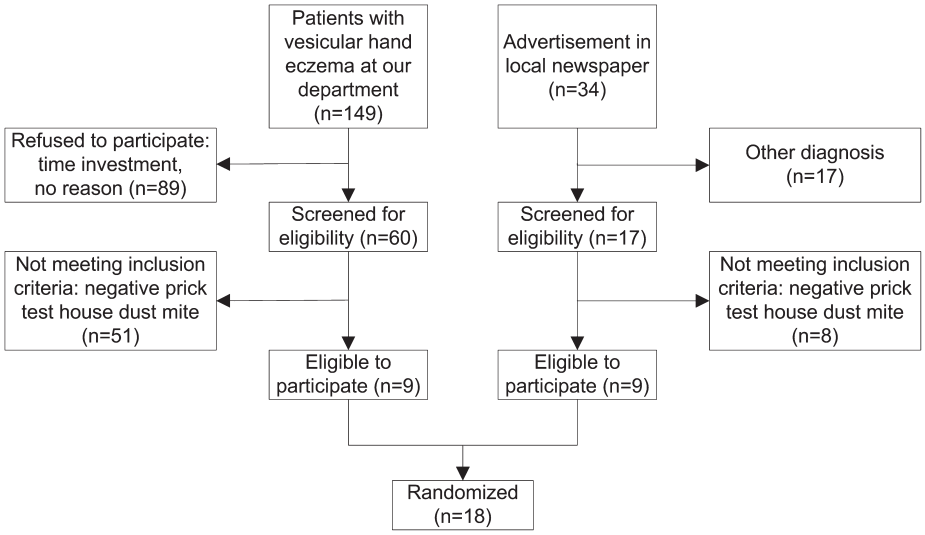

Fig. 1. Patient flow throughout the recruitment and inclusion procedure.

Table 1. The baseline characteristics of the study population

							Baseline DASI		Eosinophils (× 10^9/l)			
No.	Age (years)	M/F	History of asthma*	History of AD*	AD†	FEV_1	HDM	Placebo	HDM	Placebo	Total IgE (kU/l)	HDM-specific IgE (kU/l)
1	20	M	–	–	–	109	30	30	–	0.57	212	1.31
2	30	M	–	+	–	83	4	8	0.52	0.50	11.7	< 0.35
3	52	F	–	+	–	121	5	4	0.29	0.27	2517	11.1
4	21	F	–	+	+	106	3	16	0.71	1.13	90.2	5.64
5	43	F	–	+	+	109	43	50	0.73	0.55	1446	4.37
6	25	F	+	+	–	110	5	7	0.29	2.64	55	15.1
7	53	F	–	+	–	112	17	11	0.55	0.57	> 5000	> 100
8	23	M	–	+	–	125	8	7	0.42	0.16	117	20.9
9	60	M	–	+	–	90	16	15	0.48	0.33	52.8	0.45
10	47	F	–	+	+	112	40	40	0.26	0.17	50.6	0.82
11	50	F	–	+	+	100	28	56	0.02	0.06	81.8	0.89
12	43	F	–	+	+	99	4	2	0.12	0.11	9.5	1.90
13	48	F	–	+	+	99	16	30	0.44	0.37	219	29.50
14	26	F	+	+	+	117	0	2	0.80	0.96	407	66.20
15	24	F	+	+	+	106	0	3	0.42	0.36	708	73.70
16	57	M	+	–	–	100	0	1	0.30	0.42	67.1	1.28
17	35	F	+	–	–	92	2	2	0.13	1.43	> 5000	> 100
18	21	F	+	+	–	99	5	2	0.47	0.47	1213	>100

AD, atopic dermatitis; DASI, Dyshidrotic Eczema Area and Severity Index; F, female; FEV_1, forced expiratory volume in 1 second represented as % predicted; HDM, house dust mite; M, male.
FEV_1 (% predicted) and serum IgE levels were assessed on the first provocation day before the challenges.
*Physician diagnosis.
†Current AD according to criteria of the UK working party.

with baseline was noted after HDM provocation at 6 hr ($p = 0.045$), and, at that time point, ΔDASI was significantly different between the provocations (HDM versus placebo) ($p = 0.03$).

The median vesicles score showed significant increases from baseline at 24 hr ($p = 0.03$) and 48 hr ($p = 0.03$), but no significant differences in Δvesicles between the provocations (HDM versus placebo) were seen at these time points.

The median erythema score showed no significant increase from baseline at any time point, but Δ erythema between the provocations (HDM versus placebo)

Table 2. Median Dyshidrotic Eczema Area and Severity Index (DASI) scores [interquartile range (IQR)] and DASI sub-scores (IQR)

	Baseline	1 hr	6 hr	24 hr	48 hr
House dust mite (n = 18)					
DASI	5.0 (2.75–19.75)	5.0 (2.75–20.50)	6.0 (2.75–22.00) $p = 0.045$	6.0 (3.00–21.75)	8.5 (4.00–22.50) $p = 0.005$
Vesicles	0.5 (0.00–3.00)	0.5 (0.00–3.00)	0.5 (0.00–3.00)	1.0 (0.00–3.00) $p = 0.03$	2.0 (0.00–3.00) $p = 0.03$
Erythema	1.0 (0.00–2.00)	1.0 (0.00–2.00)	1.0 (0.00–2.00)	1.0 (0.00–2.00)	1.0 (0.00–2.00)
Desquamation	2.0 (0.75–2.25)	2.0 (0.75–2.25)	2.0 (0.75–2.25)	2.0 (0.75–2.25)	2.0 (0.75–3.00)
Itch	2.0 (0.00–2.00)	2.0 (0.00–2.00)	2.0 (0.00–2.00)	2.0 (0.00–2.25)	2.0 (0.00–2.00)
Affected area	2.0 (2.00–4.75)	2.0 (2.00–4.75)	2.0 (2.00–4.75)	2.0 (1.75–4.75)	2.5 (1.75–4.75)
Placebo (n = 18)					
DASI	7.5 (2.00–30.00)	7.5 (2.00–31.50)	7.5 (2.00–30.75)	7.5 (2.75–31.50)	7.5 (3.75–30.00)
Vesicles	1.0 (0.00–2.00)	1.0 (0.00–2.00)	1.0 (0.00–2.00)	1.0 (0.00–3.00)	1.5 (0.00–3.00)
Erythema	2.0 (0.00–2.00)	2.0 (0.00–2.00)	2.0 (0.00–2.00)	2.0 (0.00–2.00)	2.0 (0.00–2.00)
Desquamation	2.0 (1.00–2.25)	2.0 (1.00–2.25)	2.0 (1.00–2.25)	2.0 (1.75–3.25)	2.0 (1.75–3.25)
Itch	2.0 (0.00–3.00)	2.0 (0.00–2.25)	2.0 (0.00–2.25)	2.0 (0.00–2.25)	2.0 (0.00–2.00)
Affected area	2.0 (2.00–6.25)	2.0 (2.00–6.25)	2.0 (2.00–6.25)	2.0 (2.00–6.25)	2.0 (2.00–6.25)

p-values are shown only for significant differences from baseline.

was significantly different at 6 hr ($p = 0.03$) and 24 hr ($p = 0.04$).

The median itch score showed no significant increase from baseline at any time point. We expected that significant increases in the median vesicles score at 24 and 48 hr would be accompanied by an increase in itch. Table 4 shows that 6 patients had an increase in vesicles from baseline after HDM challenge at 48 hr, represented as Δvesicles 48 hr. In 5 of these 6 patients, an increase in vesicles at 48 hr was accompanied by moderate itch (2 score points) at 48 hr. In 2 of these 5 patients, the increase in vesicles was accompanied by an increase in itch of 0 score points at baseline to 2 points at 48 hr. Three of these 5 patients showed 2 score points for itch both at baseline and at 48 hr. In these 3 patients, the absence of an increase in itch may be explained by the fact that they already showed significant itch at baseline. Moreover, in 2 of these 3 patients, the increase in vesicles was not accompanied by an increase in affected area score points, which may explain the absence of an increase in itch.

Table 3 provides an overview of the number of patients who showed an increase in hand eczema after HDM provocation versus placebo provocation, and the numbers of skin responders, vesicle responders, and erythema responders. Of the DASI sub-scores, we present only the responders to the objective items erythema and vesicles, because the other items showed no significant increase in eczema as compared with baseline at the different time points. There were significant differences between the number of patients who showed an increase in eczema after HDM provocation and the number of patients who showed an increase after placebo provocation at 1 hr ($p = 0.001$), 6 hr ($p = 0.002$), and 24 hr ($p = 0.04$). Overall, there were more vesicle responders than erythema responders.

Association between bronchial reactions and hand eczema

Table 4 provides an overview of the bronchial reactions and skin response at 48 hr. In 9 of the 18 patients, the maximum dose of HDM could not be given, because of an early fall in FEV_1, varying from 16% to 35%. In total, 6 of the 18 patients had a history of asthma, and in these 6 patients the highest HDM concentration could not be given. Twelve patients showed an EAR, and 5 patients showed a LAR.

At 48 hr, there were 10 patients who showed an increase in eczema after HDM provocation, and in 7 of these 10 patients the increase in hand eczema was preceded by an EAR. In 4 of the 10 HDM responders, concomitant EARs and LARs were observed.

Twelve patients showed an EAR. At 48 hr, 6 of these 12 patients were skin responders and 6 patients were not. The difference was not significant ($p = 0.64$). There were also no significant differences at 6 and 24 hr, and no significant differences in patients with an EAR and vesicle responders or erythema responders.

Logistic regression analysis showed no significant correlation between maximum ΔFEV_1 placebo-corrected early and skin responders, vesicle responders and erythema responders at 6, 24 and 48 hr.

Five patients showed a LAR. At 48 hr, there were no significant differences in the number of patients who were skin responders or not ($p = 0.12$). There were also no significant differences at 6 and 24 hr. There were 4 vesicle responders at 48 hr; 3 of the 4 showed an LAR, and 1 of

the 4 did not. The difference was significant ($p = 0.04$). At 24 hr, there were also 4 vesicle responders; 3 of the 4 showed an LAR, and 1 of the 4 did not. The difference was significant ($p = 0.04$). At 6 hr, there were no significant differences. There were no significant differences in those with an LAR and those who were erythema responders or not at the different time points.

Logistic regression analysis showed no correlation between maximum ΔFEV_1 placebo-corrected late and skin responders at 48 hr.

Serum IgE levels and eosinophils

Patient 2 was included in the study because of a positive prick test reaction to HDM (inclusion criterion), but specific HDM IgE was not elevated.

Table 3 shows the mean levels of total IgE and HDM-specific IgE in skin responders and non-skin responders at the different time points when hand eczema was evaluated. The mean total IgE level was significantly higher in skin responders than in non-skin responders at 24 hr ($p = 0.03$). The mean total IgE level in skin responders at 6 and 48 hr was higher than that in non-skin responders at these time points, but not significantly different. The mean total IgE level was significantly higher in vesicle responders than in non-vesicle responders at 24 hr ($p = 0.02$).

The mean (SD) serum eosinophil level 24 hr after HDM challenge, 0.54×10^9/l (0.32), was significantly different from baseline: 0.41×10^9/l (0.22) ($p = 0.04$). After placebo challenge, there was no significant difference from baseline at 24 hr. The serum eosinophil level after HDM provocation and Δeosinophils (eosinophils at 24 hr − eosonophils at baseline) after HDM provocation were not significantly different between skin responders and non-skin responders at different time points. This was the same for vesicle responders.

Discussion

Our results showed that there was significantly more often an increase in hand eczema after HDM provocation

Table 3. Number of responders and mean [± standard deviation (SD)] serum IgE levels at different time points

	Assessments	1 hr	6 hr	24 hr	48 hr
HDM responders	n	3 *$p = 0.001$	5 *$p = 0.002$	8 *$p = 0.04$	10
Placebo responders	n	1	1	2	5
Skin responders	n	2	4	6	8
	Total IgE	748 (987)	1927 (2137)	2106 (2439) #$p = 0.03$	1605 (2260)
	HDM-specific IgE	3 (3)	51 (56)	38 (48)	32 (43)
Non-skin responders	n	16	14	12	10
	Total IgE	985 (1695)	682 (1404)	385 (484)	442 (515)
	HDM-specific IgE	33 (40)	23 (33)	26 (35)	28 (38)
Vesicle responders	n	0	1	4	4
	Total IgE	–	1213	2517 (2868) #$p = 0.02$	1289 (2472)
	HDM-specific IgE	–	100	54 (54)	30 (47)
Non-vesicle responders	n	18	17	14	14
	Total IgE	959 (1612)	944 (1660)	514 (734)	864 (1393)
	HDM-specific IgE	30 (39)	26 (36)	23 (33)	29 (38)
Erythema responders	n	1	2	1	3
	Total IgE	1446	1330 (165)	5000	1710 (2850)
	HDM-specific IgE	4	52 (68)	100	40 (53)
Non-erythema responders	n	17	16	17	15
	Total IgE	930 (1656)	912 (1709)	721(1296)	809 (1360)
	HDM-specific IgE	31 (40)	27 (37)	26 (36)	27 (38)

HDM, house dust mite; n, number of participants.
Total IgE and HDM-specific IgE are represented as mean kU/l (± SD). *p*-values are shown only for significant differences.
*p-values represent significant differences in the number of responders after HDM challenge and after placebo challenge.
#p-values represent significant differences in the mean total IgE level per group responders and non-responders.
Skin responders: ΔDASI after HDM > 0 and ΔDASI after HDM > ΔDASI after placebo.
Vesicle responders: Δvesicles after HDM > 0 and Δvesicles after HDM > Δvesicles after placebo.
Erythema responders: Δerythema after HDM > 0 and Δerythema after HDM > Δerythema after placebo.

Table 4. Highest house dust mite (HDM) concentration, maximum ΔFEV_1 and ΔFEV_1 placebo-corrected early and late, ΔDASI, Δvesicles, and Δerythema after HDM and placebo provocation at 48 hr

						ΔDASI 48 hr		Δvesicles 48 hr		Δerythema 48 hr	
No.	HDM concentration (BU/ml)	ΔFEV_1 early	ΔFEV_1 early P-C	ΔFEV_1 late	ΔFEV_1 late P-C	HDM	Placebo	HDM	Placebo	HDM	Placebo
1	10 000	+ 1	+ 4	− 1	+ 2	0	0	0	0	0	0
2	10 000	− 2	0	+ 1	+ 8	4	0	2	0	2	0
3	10 000	− 14	− **17**	+ 2	− 1	1	0	0	0	0	0
4	10 000	− 23	− **24**	− 14	− **16**	1	− 2	1	0	− 1	0
5	10 000	− 20	− **22**	− 4	− 8	0	− 1	0	0	0	0
6	80	− 19	− **15**	− 21	− **18**	8	− 3	3	0	0	− 2
7	2000	− 31	− **29**	− 20	− **18**	3	0	0	0	1	0
8	10 000	− 27	− **26**	− 11	− 10	1	0	0	0	1	0
9	10 000	− 5	− 3	− 3	0	0	3	− 1	1	0	0
10	10 000	− 11	− 7	− 3	+ 2	8	0	0	0	0	0
11	10 000	− 18	− **16**	− 12	− 6	3	4	1	3	0	− 2
12	2000	− 18	− **20**	− 3	− 2	0	1	0	0	0	0
13	400	− 18	− **18**	+ 1	+ 2	0	0	0	0	0	0
14	400	− 16	− 13	− 11	− 9	1	2	1	2	0	0
15	400	− 31	− **30**	− 8	− 7	0	0	0	0	0	0
16	400	− 22	− **20**	− 4	− 3	0	0	0	0	0	0
17	2000	− 35	− **32**	− 30	− **29**	4	2	2	1	0	0
18	400	− 20	− 14	− 23	− **23**	0	0	0	0	0	0

DASI, Dyshidrotic Eczema Area and Severity Index; FEV_1, forced expiratory volume in 1 second; FEV_1 placebo-corrected (% baseline) = maximum ΔFEV_1 HDM (% baseline) – corresponding ΔFEV_1 placebo (% baseline); P, placebo; P-C, placebo-corrected; ΔFEV_1, maximum percentage change from baseline FEV_1.
ΔFEV_1 P-C presented in bold: early and late asthmatic reactions.

than after placebo provocation. We demonstrated that an increase of vesicles was preceded by a LAR. Patients with an increase of the DASI had as a group a higher mean total IgE level.

From this, we conclude that HDM provocation especially induced the formation of vesicles. The clinical manifestation of a mild flare of vesicular hand eczema often begins with the formation of vesicles without inflammation or with slight inflammation. These clinical findings in vesicular hand eczema support the occurrence of mild flares after HDM provocation in our study. We also observed an early increase in erythema, which may represent vasodilatation as an early sign of inflammation.

The EAR is the result of airflow obstruction that occurs shortly after the allergen challenge by degranulation of mast cells, is maximal at 10 and 20 min or slightly longer, and resolves spontaneously by 2–3 hr. The LAR is an episode of airway obstruction that appears following spontaneous resolution of the EAR. In the LAR, inflammatory cells play an essential role, appearing approximately 4–5 hr after allergen challenge, and possibly persisting for $\geq$ 12 hr. We hypothesized that bronchial inflammation after HDM inhalation leads to a high concentration of inflammatory mediators being released into the circulation by the bronchus-associated immune system, which may subsequently lead to increased hand eczema. In hand eczema patients who were allergic to HDM, we observed that the development of vesicles was preceded by the LAR, which may also support our hypothesis. The association with the LAR is plausible, because the LAR is based on extensive bronchial inflammation (13, 14).

Although it was not a part of this study, it was noteworthy that 5 of 8 patients who started with the HDM provocation reported, at the second placebo provocation, that they had noticed an increase of eczema 4–5 days after the first HDM provocation. Four of these 5 patients had current eczema and reported more hand eczema and atopic eczema after HDM provocation, and 1 of these 5 only reported more hand eczema 4–5 days after HDM provocation. These findings indicate that the inflammatory skin response probably occurred late after allergen challenge, and that the follow-up should be extended. However, a difficulty in having a longer observation period is that confounders may affect the outcome.

We are not aware of any other study on inhalation HDM inhalation challenges in hand eczema. Brinkman et al. (8) studied allergen inhalation challenge in 16 atopic dermatitis patients, 8 with and 8 without allergic asthma, and showed a flare-up of skin lesions in both groups, and a significantly higher increase in the atopic dermatitis group with concomitant allergic asthma. They showed a significant correlation between the percentage of late fall in peak expiratory flow (3–8 hr after challenge) and the increase in atopic dermatitis. This seems to support the association

that we found between the LAR and the increase in the number of vesicles in hand eczema in this study.

We expected that, in the sample size calculation, the DASI would increase by 28 points at 48 hr after HDM provocation and that there would be no increase after placebo provocation. Our results showed an increase in the DASI of up to a maximum of only 8 points after HDM provocation in 10 patients. This was clearly less than we had expected. It is possible that we could have observed a greater increase in eczema after HDM provocation if we had used a longer post-challenge observation period. However, desquamation is an item in the DASI score that cannot contribute to the initial increase (i.e. 48 hr) when there is a mild flare. The affected area score was based on the mean percentage of affected skin, with 1 point for each 20% of affected area. In this study with only minor changes in eczema, this item was not expected to increase. At the time when we started this study, the DASI seemed to be most suitable in the absence of other validated instruments. Weistenhofer et al. (15) recently reported that, for quantifying mild skin changes, a score measured with a more differentiated scale was needed to register minimal lesions. We conclude that the DASI probably does not meet these criteria.

The degree of association between vesicular hand eczema and atopy is unclear. No association was reported in one study (2), whereas in another it was reported that atopy was a predisposing factor in the pathogenesis of vesicular hand eczema (1). We noticed that 77% of the patients with vesicular hand eczema who wanted to participate did not show a positive prick test reaction to HDM. We conducted the study in patients with vesicular hand eczema who were atopic and allergic to HDM. This group may constitute a minority among vesicular hand eczema patients. Moreover, many eligible patients were unwilling to participate. We had not anticipated this, and it was a reason why inclusion took so long.

Some limitations in the design of the study have to be mentioned. One limitation was the use of anti-inflammatory inhalation medication during the study period. Inhaled corticosteroids have systemic effects on the concentrations of circulating pro-inflammatory cytokines (16), and may interfere with the development of skin symptoms after HDM provocation. Participants with an LAR were treated with inhaled corticosteroids, owing to a fall in FEV_1 after HDM provocation, and this may have been a confounder. During the study, the patients had to continue using topical steroids or other anti-inflammatory topical medication at the same frequency and strength during the provocation, and this may have had an effect on the outcome. One patient reported an exacerbation of hand eczema, which had started some days before the start of the placebo provocation. However, she did not use clobetasol, which she normally used. Thus, the increase in her DASI score as compared with baseline after placebo provocation was unreliable. However, if she had continued using clobetasol, which is a very potent corticosteroid, it would have been a confounder.

In this study, other variables, such as allergens other than HDM allergen, could have been confounders. Although not all patients were fully screened for allergies, there were subjects with multiple sensitizations in this study. However, in most of those cases, HDM was the strongest sensitizer. In addition, exposure to HDM in this study was probably greater than the natural exposure to allergens. In 11 of 18 patients, patch tests were performed to exclude clinically relevant contact allergies.

In an outpatient setting, compliance with topical treatment is difficult to control. The question is whether patients should have been tested at the time of an exacerbation. It would be probably better to treat the hand eczema for disease control before starting with provocations.

Our test method is not completely comparable with the role of exposure to HDM allergen inhalation as it naturally occurs. In a domestic situation, HDM allergen is probably inhaled at low concentrations for prolonged periods of time. Although our study design was double-blind, the patients who experienced a decrease in FEV_1 or symptoms of dyspnoea could guess that they had inhaled HDM allergen. These patients could have reported more pruritus, which could influence the subjective item itch in the DASI score. However, we did not find a significant increase in itch after HDM challenge.

In conclusion, the results showed that hand eczema increased significantly more after HDM provocation than after placebo provocation. House dust mite inhalation challenges increased especially vesicles, which was preceded by a LAR. The group patients with an increase of hand eczema tended to have a higher mean total IgE level. These findings may contribute to a better aetiological classification of chronic hand eczema, and may have implications for the prevention of flares in a sub-group of hand eczema patients.

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