

House-dust mite hypersensitivity, eczema, and other nonpulmonary manifestations of allergy

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The pathogenetic role of house-dust mites (HDM) in atopic dermatitis (AD) remains controversial, mainly because there is no common agreement on a provocation test that mimics ordinary exposure to HDM. This is related to the lack of knowledge of the mechanism of how HDM allergens enter the body. Theoretically, there are two possible routes: directly through the epidermis, or by inhalation. In “atopy patch testing”, a concentrated HDM suspension is tested on the skin under occlusion. This method is frequently used as a model of the epidermal route. The clinical relevance of this method as a provocation test for AD is discussed. As opposed to atopy patch testing, we describe another method, namely, “allergen inhalation testing”, as a model of the respiratory route. Twenty patients with AD underwent bronchial provocations with HDM extract in a double-blind, randomized, placebo-controlled study. In nine out of 20 AD patients, bronchial challenge with HDM evoked skin symptoms. All patients with HDM-induced dermatitis had a history of asthma, and as a group they had a higher mean total log-transformed IgE level than the “negative skin responders”. Thus, the respiratory route may be relevant in the provocation of AD in a subset of AD patients and may represent an appropriate model of provocation in these patients. Furthermore, the role of HDM in urticaria and allergic rhinitis is discussed.

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Role of house-dust mites in atopic dermatitis

Atopic dermatitis (AD) is a pruritic relapsing chronic skin disease with a complex, still not fully understood, cause. Many AD patients have other atopic manifestations, such as asthma and/or allergic rhinitis, and in most there is a family history of these atopic diseases (1). Eighty percent of AD patients have a positive skin prick test, and 80% have an elevated serum IgE level (1). Strong positive reactions are most frequently obtained for house-dust mite (HDM) and pollens (2, 3). Most AD patients show positive skin prick test results with HDM (4) and increased serum levels of HDM-specific IgE (5). However, the pathogenetic role of HDM in AD remains controversial. This is mainly due to the fact that there is no consensus on a provocation test that mimics ordinary exposure to HDM. In turn, this is related to the lack of

knowledge of the mechanism of penetration of HDM allergen. Theoretically, there are two possible routes: directly through the epidermis, or by inhalation.

Atopy patch testing as a model of the epidermal route

In the last decade, attention has been focused on the epidermal route. Occlusive testing with HDM allergen elicited an eczematous reaction on abraded (6–9), scratched (10), sodium lauryl sulfate-irritated (11), or eczematous (12) skin. Testing on manipulated skin was justified by assuming that these manipulations simulate naturally occurring conditions in AD (11). More recently, positive patch test reactions were also noticed on uninvolved skin that was not manipulated (4, 8, 9, 13–15). A large-scale French study on standardization of the patch test in

AD patients not selected on HDM sensitivity has demonstrated that the percentage of positive reactions varied from 7% to 23%, depending on the source of allergens used (4). Darsow et al. found a yield of 47% positive reactions when using petrolatum as base (13). A high concordance between positive skin prick tests/specific IgE on the one hand and positive skin patch tests on the other hand was noticed (4, 9, 11, 13, 14). No positive skin patch test results were seen in nonatopics (9, 11, 13, 14). Fewer positive reactions were observed on unabraded skin than abraded skin (8, 9).

The central questions are whether or not HDM allergen can penetrate the intact stratum corneum in daily practice, and whether or not the "atopy patch test" (APT) (a term coined by Ring) is a reliable reflection of these daily life conditions. Arguments in favor of the relevance of the APT are the following: the high concordance of positive APT reactions and positive results in specific IgE/skin prick tests, which point to the allergen-specific nature of the APT. Furthermore, there are several similarities between the APT and naturally occurring AD. The appearance was described by all authors as eczematous in most cases. HDM allergens have been detected in the epidermis and dermis at APT sites and at naturally occurring dermatitis sites in AD patients (11). In both types of lesions, HDM allergens were traced to Langerhans' cells (11). Another similarity between APT and normal AD lesions is the presence of (degranulated) eosinophils and IgE-bearing Langerhans' cells in epidermis and dermis (7). In both APT and normal AD sites, acanthosis and spongiosis have been demonstrated (7, 11). An impaired barrier function, such as found in naturally occurring active AD lesions, could be induced at APT sites, but not at sites exposed to a type IV contact allergen (15), a finding which may further underline the specific nature of the APT. These similarities suggest identical ways of exposure and identical pathogenetic mechanisms, giving circumstantial evidence that the APT may be a relevant model for the induction of AD by the epidermal route. However, it must be stressed that the conditions in the APT are not physiologic, even when the skin is not premanipulated, since the concentrations of the HDM allergen in the APT are approximately 10 000 times higher than those found in the home environment. Furthermore, occlusive exposure for 24 or 48 h may facilitate HDM-allergen penetration. To a certain extent, the nature of this occlusive exposure may mimic exposure to HDM when lying in bed on a mattress infested with HDM. However, the back is a body region not frequently involved in AD. On the

contrary, it has been found that AD patients with the "air-exposed pattern" of dermatitis more frequently had a positive APT than AD patients without such a distribution (13). The APT does not mimic airborne exposure to HDM allergen. Therefore, it is difficult to imagine that airborne HDM allergens can penetrate the intact stratum corneum. On the other hand, the stratum corneum may be damaged in active AD lesions. One can hypothesize that worsening of existing dermatitis can be caused by penetration of HDM through this damaged stratum corneum. The stratum corneum in dry, nonlesional skin of AD patients differs from the normal stratum corneum with respect to water-binding capacity, barrier function, and structure (16). By scanning electron microscopy, the surface of dry atopic skin was found to be coarse and irregular (16). In this irregular stratum corneum, adherence of HDM antigens might be facilitated, possibly leading to penetration through the stratum corneum.

Allergen inhalation testing as a model for the respiratory route

The main HDM antigens are glycoproteins occurring in mite feces (Der p 1, MW 24 000) or bodies (Der p 2, MW 15 000) of *Dermatophagoides pteronyssinus* (17). The feces pellets are 10–40 µm in diameter and are easily respirable (17). Early studies support the significance of inhalation of HDM, which was shown to induce exacerbation of pre-existing eczematous lesions (18–20). Likewise, inhalation of other inhalant allergens, such as mold (18, 19) and pollens of birch (19), grass (20), and ragweed (21), caused exacerbation of AD. The occurrence of new skin lesions after inhalation of allergens was only occasionally reported (20, 22). Most authors stated the time interval between inhalation and skin symptoms as "some hours". A few authors mentioned rhinorrhea (18, 19) or bronchoconstriction (20) preceding the skin symptoms in some patients. These early studies were poorly documented and poorly controlled, and used an open-study design.

Therefore, we investigated whether it was possible to induce exacerbation of existing dermatitis or new dermatitis lesions in AD patients by means of double-blind, randomized, placebo-controlled bronchial provocations with HDM extract (23). A further aim was to study whether this dermatitis reaction was associated with bronchial symptoms. Twenty patients with AD underwent bronchial provocations with HDM. Challenge tests were performed with four concentrations of a standardized HDM extract in a double-blind, randomized, placebo-controlled fashion. Spirome-

Table 1. Mean values of characteristics in patients with cutaneous reaction ("positive responders") and without cutaneous reaction ("negative responders") after HDM inhalation

	Positive responders		Negative responders		P 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

*P value of Student's *t*-test.[†]SD (standard deviation).

DSS: baseline dermatitis severity score based on quick scoring system of Costa et al. (33) (<15, mild dermatitis; 15–30, moderate dermatitis; >30, severe dermatitis); log-eo: log₁₀-transformed eosinophil count; log-total IgE: log₁₀-transformed total blood IgE level; log-HDM-IgE: log₁₀-transformed house-dust-mite-specific IgE level, using CAP radioallergosorbent test (Pharmacia).

try was performed, and forced expiratory volume in 1 s (FEV₁) was measured before and after each challenge dose. Changes in severity or localization of itching or erythema were recorded.

In nine out of 20 AD patients, bronchial challenge with HDM evoked unequivocal skin symptoms after 1.5–17 h. Pruritic erythematous lesions on noninvolved sites, together with exacerbation of existing lesions, were seen in three patients. Three patients had exacerbation only and three other patients had new lesions only. In 8/9 patients with HDM inhalation-induced dermatitis, skin symptoms were preceded by an early bronchial reaction. All patients with HDM-induced dermatitis had a history of asthma and, as a group, they had a higher mean total log-transformed IgE level than the "negative skin responders" (Table 1). The positive skin responders tended to have higher dermatitis severity scores before provocation, higher log-transformed eosinophil count, and higher log-transformed HDM-specific IgE. One patient had pruritic erythema on the placebo challenge day without a preceding bronchoconstrictive reaction.

From these results, it was concluded that the respiratory route may be relevant to the induction and exacerbation of dermatitis in a subset of AD patients who had early bronchial reactions after HDM inhalation, history of asthma, and elevated blood total IgE level. Furthermore, these findings suggest a possible causal relationship between bronchial and skin reactions.

Others have also recently demonstrated a deterioration of dermatitis in six AD patients with asthma, and six AD patients without asthma upon inhalation of HDM (24). The increase in the dermatitis severity score ("Costa score") was significant in the group of AD patients with asthma (24).

The conditions in experimental bronchial allergen inhalation are not the same as those met in

daily life (25). It is stated that the natural exposure represents a very limited number of particles, each of which carries a much larger quantity of allergen than the droplets used for provocation (25). It is assumed that during natural exposure, local foci of inflammation are produced and that clinically significant bronchial reactivity would only occur with repeated exposure during a period of days or weeks (25).

Role of house-dust mites in urticaria

Some patients develop a pruritic erythematous reaction at the APT site within 20 min (4, 7, 9, 10, 12). Urticaria has been described in HDM-allergic patients with allergic rhinitis (AR) and asthma who were treated with HDM injections for immunotherapy (26, 27). Occasionally, patients have been described who have acute urticaria on dust exposure, and are found to be allergic to HDM (25). We observed a patient with AD, AR, and asthma who developed pruritus, rhinitis, and dyspnea immediately after bronchial inhalation of HDM (not published). One hour after inhalation, the pruritus was accompanied by widespread erythematous areas. These areas were not edematous, as in urticaria. No immediate-type skin reactions were observed in our double-blind, placebo-controlled study (23).

Role of house-dust mites in allergic rhinitis (AR)

There are several recent large-scale epidemiologic studies on the prevalence of AR and sensitization to indoor and outdoor allergens. A study performed on schoolchildren in Hong Kong, San Bu (China), and Malaysia showed a prevalence of AR varying from 3.7% in San Bu to 29.8% in Hong Kong (28). HDM and cockroach were the two most common inhaled allergens found at all locations. HDM allergy was an

independent risk factor for AR and asthma (28). In a recent Dutch cross-sectional study, the prevalence of self-reported rhinitis symptoms was 29.5% (29). More than 50% of these self-reported rhinitis patients had positive results in skin prick test and/or specific IgE test. HDM was the most prevalent allergen, as demonstrated by skin prick tests and specific IgE (29). Cat, dog, HDM, and grass were the allergens most frequently found in a Canadian study on patients with AR and/or asthma (30). Among patients sensitized to indoor allergens, 48.6% had AR, 24.5% had asthma, and 26.9% had AR and asthma (30).

Rhinitis symptoms were observed immediately after nasal challenge with HDM and 3.5–8.5 h after challenge (late-phase reaction) (31, 32). Patients having early- and late-phase symptoms were characterized by a higher nasal responsiveness to histamine and increased production of leukotrienes during the early response, when compared with patients without a late-phase reaction (32). These findings point to a causal relationship between AR and HDM allergen.

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