Mite allergy and atopic dermatitis: Is there a clear link? (Review)

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Abstract. Atopic dermatitis (AD) represents a widespread chronic skin disease associated with different atopic disorders and allergies. These associations, similar to overall AD pathophysiology, are entangled, multifactorial and they are yet to be clarified. IgE and non IgE mediated pathomechanisms appear to be implicated in AD. Allergens constitute key aspects in AD pathogenesis, as they may serve as trigger factors. This review emphasizes mainly house dust mites (HDM), as they are likely the most relevant airborne allergen for AD. Here we review in a concise form the mite allergens, the role of molecular diagnosis and the treatment strategies for HDM. Strategies of avoiding allergens, with a few exceptions, are not enough to control children's AD; recent studies show HDM avoidance procedures in diagnosed AD are insufficient. Regardless, some guidelines acknowledge the benefit of mattress and pillow covers in patients with dust mite sensitization that are unresponsive to optimal AD management. Most clinical trials investigating allergen-specific immunotherapy (AIT) as a potential treatment for AD were done with adult patients; a scarce number of studies looked into the efficacy of AIT as a treatment option in children suffering from AD, with conflicting data among them. One of the most feasible of these studies showed significant improvement of AD outcomes only in the mild/moderate group, but not in the severe group. Uncontrolled studies are hard to interpret, considering the natural history of remitting and relapsing of AD, in many of the patients, without clinical interventions. More AIT studies, especially pediatric studies, are required in order to either prove the reproducibility of positive results or to deny its effectiveness.

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Abreviations: HDM, house dust mite; AD, atopic dermatitis; AIT, allergen *b*-specific immunotherapy

Key words: atopic dermatitis, mite allergens, molecular allergology, avoidance strategies, allergen-specific immunotherapy

Contents

1. Introduction

Atopic dermatitis (AD) represents a chronic pruritic, remitting-relapsing inflammatory skin disorder, often linked with other symptoms of IgE-associated allergy, for instance allergic rhinoconjunctivitis, allergic asthma and IgE-mediated food allergy. In fact, it is frequently the first step in the sequential development of the other different atopic conditions; this is called 'atopic march' (1).

AD constitutes a global issue that affects 5-20% of the pediatric population and 2-8% of adults, frequently beginning in infancy (2-6).

This complex disorder, most likely relies upon an interaction between the genetic predisposition, the skin barrier disruption, an inappropriate immune response and an abnormal microbial skin colonization.

Airborne allergens can be specific trigger factors; therefore, they are essential in AD pathogenesis. For instance, exacerbation of AD can be observed in patients during allergen exposure (7). Thus, based on the presence or the absence of detectable allergen-specific IgE antibodies, AD can be either extrinsic or an intrinsic (8). However, there is another subgroup of AD patients with autoimmune IgE-mediated reactivity against auto-antigens in addition to sensitization against airborne allergens (9).

Nonetheless, in most of the AD patients IgE sensitization is present. Only some forms (intrinsic AD) were not associated with disease exacerbating allergens. Patients suffering from

AD are frequently polysensitized to many different airborne, food-derived, microbial allergens and autoallergens (10).

AD patients have an impaired baseline-epidermal barrier function, which can result from decreased and dysfunctional structural proteins (e.g., filaggrin, claudins) and altered lipid composition (especially ceramides). This altered barrier function grants airborne proteins, microbes and other irritants easy access into the epidermis; so they can interact with local immune cells to initiate the type I-immediate and type IV-delayed hypersensitivity reactions that are common in AD patients (11).

This review mainly emphasizes house dust mites (HDM), since they are likely the most relevant airborne allergens for AD. We reviewed mite allergens, molecular diagnosis and the treatment strategies for HDM (allergen avoidance and allergen specific immunotherapy).

2. HDM allergens

House dust contains numerous species of mites; nevertheless, only three of them are very common in homes worldwide: *Dermatophagoides pteronyssinus* (Der p), *Dermatophagoides farinae* (Der f) and *Euroglyphus maynei* (Eur m). They can be found in temperate climate, but it is also important to mention *Blomia tropicalis* (Blo t) that is prevalent in tropical and subtropical climate.

There are four other species of storage mites (Acarus siro, *Glycyphagus domesticus, Lepidoglyphus destructor, Tyrophagus putrescentior*) in house dust from farms or in food storage (12).

They have a life cycle of ~3 months that includes several stages of development from egg, larva, protonymph, tritonymph to adult which measures ~1/4 to 1/3 of a millimeter in length (13).

In order to maintain their metabolism, reproductive rate, and allergen production, dust mite species need special temperature and humidity conditions, as well as low light. Because they are constituted of nearly 75% water by weight, they need to maintain their water balance through uptake of water vapor from indoor environment. Their optimal humidity level to proliferate and survive is ~75%; reducing indoor humidity represents a common strategy to reduce their number (14).

Dust mites feed on organic materials, including skin scales, fungi, yeasts, and bacteria. Not only live mites cause allergic reactions, but also their faeces and remains. They produce and excrete numerous allergens into the environment (15).

Numerous mite allergens have been described and have been classified in specific groups (1-39) based on their biochemical composition, sequence homology, and molecular weight. The allergen designation is made by using the first 3 letters of the genus followed by the first letter of the species and the group number. Thus, allergens for the three most dominant species are Der p 1 to Der p 38, Der f 1 to Der f 39, and Blo t 1 to Blo t 21 (12). Because it is difficult to characterize such a large number of allergens, details are summarized in Table I including the biologic function and specific characteristics for the most important, major and relevant minor allergens of Der p and Der f.

Allergens from group 1 (Der p 1 and Der f 1) and group 2 (Der p 2 and Der f 2) represent major allergens, based on the frequency of patient sensitization and the amount of specific IgE (16). At present, Der p 23 represents another major allergen (17). Groups 4, 5, 7, and 21 allergens are considered as mid-titer allergens and Group 3, 6, 8, 9, 10, 11, 13, 15, 16, 17, 18 and 20 are considered minor allergens, because of their low IgE-binding capacity; of the group 10 allergens, Der p 10 has a particular significance, being responsible for cross-reactivity with crustaceans and cockroaches (16).

Airborne allergens derived from HDM are eliciting AD. Due to their enzymatic activity, allergens are found to destroy tight junctions and deteriorate the skin barrier function in patients with AD (18). This perturbation of skin barrier allows proteins from airborne allergens to penetrate into the epidermis, reach allergen-presenting dendritic cells, prime the Th2 allergic systemic inflammatory response and worsen AD severity. Activation of PAR-2 (proteinase-activated receptor-2) in epidermal keratinocytes and dermal nerves as a result of protease activity has an important role generating histamine unrelated pruritus (19), delaying healing and recovery of skin barrier function (20) and cytokine releasing in AD (21).

Mite allergens can promote sensitizations to other allergens as a result of proteases disrupting the skin barrier. Also, it seems that IgE antibodies against a single antigen can enhance the formation of IgE to other antigens as a result of CD23 effect on epithelium and B cells and also by upregulating the high-affinity IgE receptor FcεRI (22).

Independent of sensitization, mite extracts can induce pro-Th2 cytokines IL-25 and IL-33 via the activation of TLR1/6 signaling (23).

Upon dust exposure, up to one-third of AD patients who tested positive to HDM have reported aggravation of eczema or respiratory symptoms (24). Studies regarding the connection between HDM allergens and AD have a long history. In 1949, Tuft (25) revealed that the reduction of HDM levels could determine a favorable evolution in atopic eczema patients. The exact mechanism by which exposure to HDM results in worsening of eczema is still unclear; nevertheless, when patients with eczema are patch tested with HDM, CD4 + T cells specific to HDM are found in the patch of skin that has developed eczematous characteristics (26,27).

3. Molecular diagnosis

Using recombinant allergens in order to establish the molecular diagnosis has greatly improved allergen characterization and the knowledge of pathomechanisms causing allergic diseases. Molecular allergology allows a good view on the risk associated with sensitization. Allergenic components are measured individually to determine the exact molecular level of the component to which the patient is sensitized. Considering this aspect, allergen extracts are being gradually replaced by allergen components. The novel developments will allow clinicians to acquire thorough data on the sensitization patterns and a more precise interpretation of the allergic symptoms. In this respect, molecular allergology is a great example of the association between precision medicine and allergy. A recently published guide highlights all the advantages of molecular diagnosis (12).

Table I. Major and relevant minor mite-allergens for D. pteronyssinus and D. farinae species. Adapted from The role of dust mites in allergy by Miller JD in Clin Rev Allergy Immunol 57 (3): 312-329, 2019 and EAACI molecular allergology user's guide by Matricardi PM, *et al* in Pediatr Allergy Immunol 27 (Suppl 23): 1-250, 2016.

Groups	Allergenic molecule	Biologic function	Allergic significance	Prevalence among patients (%)
1	Der p 1 Der f 1	Cysteine protease	Major allergen. PAR activator	70-100
1	Der p 2 Der f 2	Lipid binding	Major allergen. Homologous to MD-2, the LPS-binding link to TLR4	80-100
3	Der p 3 16-100 Der f 3	Serine protease (trypsin)	PAR activator	
4	Der p 4	Amylase		25-46
5	Der p 5	Lipid binding		50-70
6	Der p 6	Serine protease (chymotrypsin)	PAR activator	8-41
7	Der p 7 Der f 7	Lipid binding		50
8	Der p 8 Der f 8	Glutathione transferase		40
9	Der p 9	Serine protease (collagenase)	PAR activator	
10	Der p 10 Der f 10	Muscle tropomyosin	Responsible for shrimp cross-reactivity	5-18, 50-95
11	Der p 11	High molecular weight muscle paramyosin	Major allergen in atopic dermatitis	80
23	Der p 23	Peritrophin, chitin binding	Major allergen	74

PAR, protease-activated receptor; LPS, lipopolysaccharide; TLR4, toll like receptor 4.

By using recombinant technology, it was revealed that sensitization to particular allergen molecules or to a combination of allergens is more common for some allergic diseases than for others. Thus, Der p 11 and Der p 18 (associated with mite bodies) are more frequently recognized by IgE antibodies from patients with AD (28,29) whereas mite allergens associated with fecal particles (Der p 1, Der p 2, Der p 5, Der p 23) are more frequently recognized by patients with respiratory allergy (30,31). Two explanations of these findings may be taken into account; first is that there could be different routes of sensitization in AD and respiratory allergy and the second is that AD patients may react with a more polyclonal response, which includes less commonly recognized allergens, such as the HDM body-derived allergens. Thus, the latter, may sensitize through the skin.

In a recent survey (32), a comprehensive panel of allergen molecules from exogenous allergen sources were used, i.e. microbes and autoantigens, in order to describe the molecular IgE reactivity profile of AD patients with defined clinical phenotype. The results confirmed earlier findings (9,33) showing that AD patients are more frequently sensitized to microbial allergens such as *Malasezzia* spp, *S. aureus* and *E. coli* and also to autoallergens. It was also found that patients with more severe forms of AD recognize a greater proportion of the allergen profile (including HDM allergens) in comparison to patients with moderate forms. This very interesting finding can be explained by the fact that the severity of AD may depend on the number of different allergen molecules recognized; this is similar to earlier results of a respiratory survey: Children with more severe respiratory symptoms (rhinitis and asthma) reacted to a larger panel of HDM allergens compared with children suffering from rhinitis only (30). An explanation can be that patients with more severe AD and broader IgE recognition profiles may be more 'atopic' than patients with moderate AD (32). Earlier studies (34) have shown that patients with poly-sensitization to airborne allergens differed from monosensitized patients by their production of IL-4 and Th2 driven cytokines. In this scenario, Bousquet *et al* (35) proposed the hypothesis that polysensitization is associated and related to the persistence and occurrence of fetal Type 2 signaling. Data obtained by the above authors in the MeDALL (Mechanisms of the Development of ALLergy) project seem to confirm that patients with AD are often polysensitized towards a large number of different allergen molecules and thus exhibit extremely complex IgE sensitization profiles.

Therefore, molecular diagnosis can provide a basis for further research, exploring the genetic and environmental factors that could be responsible for different severity of AD phenotypes leading to improved disease management following the principle of personalized medicine approach.

Characterization of allergen sensitization might be improved by newer techniques for the determination of IgE reactivity using microarrays (36).

4. Reducing exposure to house dust mites

The effectiveness of interventions that reduce or avoid exposure to HDM in patients with AD is still uncertain. The results of the recently published large birth cohort study by Posa *et al* (37) demonstrated that children growing up under conditions of low exposure to HDM are less likely to develop HDM allergy; thus, recommending HDM allergen avoidance in order to prevent allergic sensitization at least in children with AD should be considered. Different data were provided by a meta-analysis (38) that investigated the role of dust mite avoidance in primary prevention of AD; the conclusions were that HDM avoidance strategies do not decrease the risk of developing AD in high risk infants compared with randomized controls.

Although its efficacy has not been proven, giving the increased prevalence of aeroallergen sensitization in patients with AD, especially older children and adolescents, HDM avoidance is commonly recommended by many clinicians in order to prevent and treat AD. Many interventions aim the reduction of exposure to dead or alive HDM and their faeces. Physical interventions include barriers (mattresses, duvet and pillows encasings), frequent vacuuming, changing floor covering, changing relative humidity (e.g., ventilation), air filters, ionizers, heat exchangers, removing soft furnishing, removal of soft toys, washing (55 degrees Celsius or higher) (11). Chemical interventions include acaricide sprays (26,39). Their usage is generally focused on the bedroom of the affected person; there is no information regarding the usefulness of these strategies outside the home, but it could be taken into consideration, since people with AD can spend many hours in other environments such as school or work. A combination of methods may be used, especially in case of severe flares or high HDM levels (39). Furthermore, rehabilitation programs in mite free environments, like in alpine climate, have shown to lead to significant and long-lasting improvement of AD (40).

Irrespective of medical advice, families often assign a significant amount of expences to HDM control measures; many of these interventions have few or not known adverse events (41) compared with other treatments, such as topical corticosteroids, which can potentially generate side effects and consequenly, an inappropriate level of fear of using pharmacological treatment (42-44). An evidence-based approach is essential in order to highlight any potential benefit or harm of these interventions.

Some studies have shown a clear-cut benefit from HDM avoidance strategies in the improvement of AD (45,46). A recent meta-analysis (47) was not in favor of HDM avoidance strategies in diagnosed AD. It was designed to assess the effects of all HDM reduction and avoidance measures for the treatment of eczema. Randomized controlled trials (RCTs) of any HDM pharmacological and non-pharmacological interventions in eczema patients were included. The comparators were any active treatment, no treatment, placebo or standard care only. Generally, the included studies had a high risk of bias. Four of the seven trials tested multiple interventions and three tested only one intervention. The Cochrane review could not offer clear implications for clinical practice due to the very low-quality evidence currently available. The limited treatment responses that occurred were in atopic patients with sensitivity to one or several aeroallergens.

Overall, the use of all HDM avoidance strategies in eczema population as a whole is yet unclear. High quality long-term trials of single, easy to apply house dust mite reduction or avoidance measures are needed.

The guidelines are not aligned in supporting the HDM avoidance strategies. The Consensus-based European Guideline for treatment of atopic eczema, part I (2) recommend HDM avoidance strategies to be used for selected cases of AD. According to the American Joint Task Force (JTF) (5) guidelines, minimizing the exposure to aeroallergens (such as: Animal dander, HDM and pollens) is highly recommended particularly by HDM in AD patients. Moreover, they recommend the use of house dust mite mattress and pillow covers based on multiple studies highlighting their successful reduction in house dust mite sensitization levels. Although the American Academy of Dermatology (AAD) attests to the reduction in house dust mite sensitization, they emphasize the limited and controversial evidence of mattress and pillow covers in reducing AD severity (48). The AAD actually advises against thr routine use of house dust mite covers in patients with AD without proven allergen sensitization. This group acknowledges the potential benefit of mattress and pillow covers in patients with proven dust mite sensitization, refractory to optimal AD management, citing greater clinical improvement in this subset of patients in one clinical investigation (48).

5. Allergen-specific immunotherapy (AIT)

AIT has been considered for AD treatment. The two therapeutic options are subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). In respiratory allergic disorders, AIT is important for both the treatment and the prevention of future sensitization and progression to more severe respiratory disease (from rhinitis to asthma). There is a large amount of data supporting this assertion. The data showed that AIT can be used for the treatment of allergic rhinitis and mild asthma in AD patients also, since AD did not worsen and sometimes improved during or after AIT (49-51). Hypothetically, an AD patient with a positive atopy patch test and corresponding history of eczema flares may be a candidate for AIT with the respective allergen.

So far, only AD patients with IgE hypersensitivity confirmed by allergy tests (skin prick tests or serum specific IgE) have been investigated. IgE constitutes the basis of literature in the area, and while encouraging results have not been obtained yet, the answer may lie elsewhere. A study of AIT in pollen allergies (52) shows that a ratio of IgG4 to IgG1 can be used to predict outcomes better than IgE, the latter being an unreliable biomarker due to variability and great fluctuation over time, poor positive predictive value for clinical relevant allergy and poor correlation with disease state. Attempting to focus on one potential HDM allergic exacerbation of AD, without a clear understanding of the role the allergens play in the complex pathophysiology of AD, does not seem favorable at this time.

The majority of clinical trials investigating AIT as a potential treatment for AD only concentrate on HDM-AIT (49,53). Most of them are in adult patients; the efficacy of AIT as a treatment option in children with AD has been the subject of few studies, with conflicting data among them. A well performed randomized controlled trial (RCT) was conducted by Pajno *et al* (54). The inclusion criteria of this 18-month study allowed patients to be sensitized to pollen or food allergens, however, any patient with a clinically significant allergen other than HDM was excluded. At the end of the study, there was important improvement in both SCORAD (standardized clinical severity scoring system for AD) and in use of rescue medication in the active sublingual immunotherapy (SLIT) group when compared with placebo control, but the significant difference was only seen in the mild/moderate group and not in the severe group. Thus, the inefficacy of SLIT in children with severe AD can be a major concern since atopy and IgE sensitization appear to play a larger role in severe AD cases. Other pediatric studies focusing on SLIT (55) and on subcutaneous immunotherapy-SCIT (56) did not show any clinical benefit.

More AIT pediatric studies are required, in order to prove reproducibility of positive results or to deny its efficacy. HDM-AIT has gained more attention for pediatric AD; SLIT is better tolerated, with fewer (local mucosal) adverse effects than SCIT and with better compliance (57). However, without any kind of meta-analysis, impossible with these smaller, heterogeneous pediatric trials, AIT cannot be generally recommended in pediatric AD. We are still waiting for new criteria or the selection of appropriate population; the frequent polysensitization contributes to a difficult interpretation of the clinically relevant allergen, suitable for AIT. Last but not least, the time and effort not attributed to skin targeted therapy could negatively impact the pediatric AD outcomes.

A large RCT investigated 168 adult AD patients during 18 months (58). According to the study, there was no efficacy of the HDM-AIT in the AD patients included; however, a subgroup analysis displayed statistically significant SCORAD reduction in a subgroup of severe patients (SCORAD >50). A higher efficacy was linked to a treatment administered during a longer period of time. A meta-analysis of eight RCT trials published by December 2012 determined the efficacy of AIT for AD (59). The results showed that AIT has a significant positive effect on AD patients, with significant efficacy in long-term treatment (OR, 6.42; 95% CI, 1.31-7.48) for severe AD (OR, 3,13; 95% CI, 1.31-7.48) and when administered subcutaneously OR, 4.27; 95% CI, 1.36-13.39). Nonetheless, these results were based on an analysis of small number of patients, included in clinical trials with considerable heterogenicity.

The Consensus-based European Guideline for treatment of atopic eczema, part II (60) does not currently recommend AIT as a general treatment option for AD. It can be taken into consideration for selected patients with HDM sensitization, who also have severe AD and a history of clinical exacerbation after exposure to the causative allergen or a positive corresponding atopy patch test. The American JTF guidelines assess AIT, and suggest that a clinician can consider immunotherapy in selected patients with aeroallergen sensitivity (5). This recommendation is based on its usefulness in patients that were diagnosed with AD, associated with clinically relevant aeroallergen sensitization. On the other hand, the AAD guidelines reviewed the literature for both sublingual and injection immunotherapy concluding that the available information does not support recommendation for use at this time.

6. Conclusions

HDM allergens are the most relevant airborne allergens for AD. Molecular profiling towards allergen components has proven to be very useful in the diagnosis management of patients with AD, guiding new forms of personalized treatment based on different disease phenotypes. Furthermore, molecular allergology will help with the proper selection of AD patients for IgE-targeting, for allergen avoidance and AIT.

Actual data on allergen avoidance have shown that, with some exception, it is generally not effective in controlling AD in children; a recent meta-analysis was not in favor of HDM avoidance strategies in established AD. Regardless, some guidelines acknowledge the possible benefit of mattress and pillow covers in patients with proved dust mite sensitization refractory to optimal AD management, citing greater clinical improvement in this subset of patients in one clinical investigation. High quality long-term trials of single, easy to apply house dust mite reduction or avoidance measures are needed.

The majority of clinical trials looking into allergen specific immunotherapy (AIT) as a potential treatment for AD were carried out with adult patients; the efficacy of AIT as a treatment modality in children with AD has been the subject of few studies, with conflicting data. A well-performed study showed significant improvement of AD outcomes only in the mild/moderate group and not in the severe group. Uncontrolled studies are difficult to interpret, due to the natural history of remitting and relapsing of AD over time, in many patients, without clinical interventions. More AIT studies, especially pediatric studies, are required in order to either prove the reproducibility of positive results or to deny its efficacy.

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Authors' contributions

RSB, DB and SLC contributed to the acquisition of the data, the conception and the design of the study. SA, LCD and ISF contributed to the analysis of the data. All authors were responsible for drafting and revising the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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