



House Dust Mite-Induced Allergic Rhinitis: Is Prevention an Option?

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Abbreviations AR Allergic rhinitis · HDMs House dust mites · HDM-AR House dust mite-induced allergic rhinitis · GINA Global Initiative for Asthma · IgE Immunoglobulin E · Th2 T helper cell type 2

Abstract

Purpose of review The aim of this paper is to review and summarise the current knowledge of prevention of house dust mite (HDM)-induced allergic rhinitis (AR).

Recent findings AR can be either classified as seasonal/intermittent (for example hay fever occurring summer and autumn) or perennial/persistent (occurring throughout the year). The commonest trigger for seasonal AR is pollen whereas HDMs are the key allergic trigger for perennial AR. HDMs are a recognised indoor allergen that is crucial in the development of AR, asthma, and atopic dermatitis.

Summary Preventive strategies have gained acceptance for the management scheme in the treatment of patients with AR. Specifically, preventive measures include allergen avoidance, environmental control, and immunotherapy. The primary goal of medical treatment is to reduce the burden of disease, improve quality of life and to prevent the development of the sequelae of AR such as bronchial asthma. Prevention is a viable option and key component in HDM-AR management. As urbanisation and lifestyle changes lead to the increase of HDM-AR, there should be a more concerted effort towards prevention.

Introduction

Allergic rhinitis (AR) is currently acknowledged as a major public health problem worldwide with its prevalence varies between 15 and 50% in different populations [1–3]. This large discrepancy in terms of prevalence and incidence in different parts of the world could be due to under-reporting of the disease as those with mild AR do not seek treatment [3]. The association between asthma and AR is well recognised. Up to 85% of asthmatic patients have AR whilst 15 to 38% of AR patients have asthma [4••, 5]. AR is also closely associated with other allergic disease such as atopic dermatitis whereby 85% of atopic dermatitis patient have rhinitis symptoms [6].

AR can be either classified as seasonal/intermittent (for example hay fever occurring during summer and autumn) or perennial/persistent (occurring throughout the year). The commonest trigger for seasonal AR is pollens whereas house dust mites (HDMs) are the commonest allergic trigger for perennial AR [7•]. HDMs are a recognised indoor allergen that is crucial in the development of AR, asthma, and atopic dermatitis [8•, 9]. Pyroglyphidae species of HDMs, namely *Dermatophagoides pteronyssinus* (Der p) and *Dermatophagoides farina* (Der f) are the most common allergens responsible for allergic diseases [10]. The prevalence of sensitisation to these mites is reported to be from 8 up to > 90% in different countries [10]. Understanding their habitat, diets, life cycle, and reproduction is essential in order to promote or suppress the growth of population of HDMs in the prevention of AR.

Megatrends such as climate change, rapid human population growth, and urbanisation might impact this increase of prevalence of allergic airway disease [11]. The rise in humidity and temperature because of climate change promotes the growth of HDMs. Besides that, urbanisation causes the release of diesel exhaust particles which are the main components of traffic-related air pollutants [12]. Diesel exhaust particles have the ability to bind to HDM allergens, facilitate allergen entry into

the airway, and consequently induce immunological response of allergic airway disease [12].

House dust mite-induced allergic rhinitis (HDM-AR) is an Ig-E-mediated immune response occurring in the mucosal lining of nasal cavity, manifested by classical rhinitis symptoms (sneezing, nasal itchiness, rhinorrhea, and nasal congestion) and/or ocular symptoms (itchy, teary, and red eyes) [4••], with positivity of sensitisation to HDMs during skin prick test or nasal provocation test and/or high specific IgE titre to HDMs [13•].

The variable symptoms of HDM-AR from mild to severe reflect the coping ability and strategy of immune system in overcoming the trigger mechanism. It becomes more troublesome when combined with symptoms of allergic asthma as both upper and lower respiratory tract are affected [14]. Approximately 93% of moderate-severe AR patients seek treatment from general practitioner [15] and 18–48% had uncontrolled symptoms by medical therapy [14]. AR gives impact to the patient's daily routine, social life, school, sports, and work performance thus burdening the society as well as the healthcare system.

Management of HDM-AR consists of symptom control measures and more importantly, the preventive measures. Currently, there is no specific guideline in managing HDM-AR whereas there are known guidelines in treating AR and asthma such as Allergic Rhinitis and its Impacts on Asthma (ARIA) [4••] and Global Initiative for Asthma (GINA) [16] guidelines, respectively. ARIA guidelines recommend minimising early life exposure to HDM among infants and pre-school children in treating AR [4••]. In clinical practice, any preventive strategy should be practical, feasible, and cost effective. In order to implement effective preventive strategies for HDM-AR, we need to understand its mechanism and risk factors as well as available treatment options. In this review, we discussed the mechanism, risk factors, pharmacotherapy, and prevention strategies of HDM-AR.

Mechanism of house dust mite allergy

Direct correlation between HDM-mediated allergies and the level of exposure to the HDMs during early life especially the first 3 years of life was previously described [17, 18]. However, the mechanism of silent sensitisation and its translation into symptomatic disease is not well described. Some studies

showed that the sensitisation does not follow the linear pattern of exposure which is described as a bell-shaped dose-response curve [19–21]. Thus, the 'high-dose tolerance phenomenon' in HDMs allergy is unexplainable.

To understand the mechanism of HDMs allergy, it is important to know the life cycle of the HDMs itself. The female HDMs usually lay around 40 to 80 eggs and HDMs will reach adulthood in 3 to 4 weeks with life expectancy between 4 and 6 weeks [22]. Keratin from human skin scales is the most important component in the dust as the primary food source. The allergenic digestive enzymes excreted in its faecal pellets consist of the dissociated digestive cells from the gut wall that binds to ingested food [22].

Disruptions of T helper (Th) balance significantly increase the allergic manifestation in HDM-mediated allergy. The allergenic effects of HDMs are divided into two phases mediated by CD₄ Th2 cells which induce the IgE-mediated allergic response and the innate immune system [23, 24]. The pathophysiology in the activation of the immune system follows the common pathway of the mechanism of allergic rhinitis. The HDM allergen components that can induce sensitisation can be divided into serodominant allergens (group 1, 2, and 23 allergens) that has more than 70% of IgE binding with high IgE-binding strength, mid-tier allergen (group 4, 5, 7, and 31 allergens) which has 30–40% of IgE binding, minor allergens (group 3, 6, 8, 9, 10, 11, 13, 15, 16, 17, 18, and 20 allergens), and allergens of unknown importance (group 14, 22, 24, 25, 26, 27, 28, 29, 30, 31, 32, and 33 allergens) [25, 26]. These allergens have different biochemical denomination and biological activities that contributes to the activation of the immune response. The biological activities and allergenicity descriptions of each of the HDMs groups are extremely complex and can assist in the development of new types of immunotherapy and identification of cross-sensitisation.

Group 1 and 2 components of HDM allergen are not species specific and capable to activate multiple routes of immune response. The main biochemical component in group 1 is cysteine protease of which the main biological activity is proteolysis [25]. The effects on immune system includes production of cytokines, chemokines, collagens, pro-Th2 and growth factors, degranulation of mast cells and eosinophils, fibroblast maturation, smooth muscle proliferation, airway remodelling, and direct damage to respiratory epithelial cells [17, 27]. Group 2 has different effects compared with group 1. The biochemical denomination of group 2 is ML domain protein and the biological activity is lipid binding including lipopolysaccharide [25].

The mechanism of AR starts when the allergen deposited and eluted in the mucous layer of the respiratory epithelium. The early phase response lasts for about 2 to 3 h. The allergen is taken up by the allergen presenting cells and activates the Th lymphocytes to release cytokines and B lymphocytes for the synthesis of allergen specific IgE. The allergen specific IgE binds to the receptor on the mast cell causing degranulation of mast cell to release inflammatory mediators such as histamine, tryptase, chymase, kininogenase, and heparin [28, 29]. In addition, mast cells also secrete de novo mediators such as prostaglandin D₂ and all 3 cysteinyl leukotrienes (LTC₄, LTD₄, and LTE₄) [29]. The end result of mucosal oedema, rhinorrhoea, and blood vessels dilatation leads to nasal congestion. Simultaneously, stimulation of the sensory nerve fibres and systemic reflexes by the mediators causes itchiness and sneezing, respectively. The late-phase response causes prolongation of symptoms that lasted for about 18 to 24 h. This response is due to inflammatory cells (T lymphocytes, basophils,

eosinophils, neutrophils, and macrophages) influx promoted by the chemoattractant cytokines, such as IL-5 [28, 29]. These cells will release variety of inflammatory mediators such as leukotrienes, histamine, and kinins causing prolongation of symptoms. Th2 lymphocytes release IL-3, IL-4, IL-5, and other cytokines that stimulates the IgE production, eosinophil, and recruitment of mast cells. The cytokines released will circulate to the hypothalamus causing neurocognitive deficit, malaise, fatigue, and irritability [29].

Risk factors of house dust mite allergic rhinitis

Some of the theories of the risk factors of HDM-induced AR are still debatable. Some did suggest that early exposure to allergen is important for immune tolerance and long-term prevention of allergy development. However, study by Baiz et al. is the first in the literature stating that early exposure to HDMs allergens contributes to the development of allergic sensitisation in asthma and AR in children [30]. In their study, they quantified the level of Der p 1 allergen by ELISA in breast milk of 255 mothers and found that presence of Der p 1 allergen in breast milk above the median value had a significant increased risk of allergic sensitisation at 5 years old as compared with children breast-fed by mothers with Der p 1 allergen in breast milk below the median value. A cohort of 1314 new-born was followed up prospectively until 3 years old in a study in German and found a dose-response relationship between HDMs allergen levels and development of sensitisation in the first 3 years of life [18]. They found that in the homes of children who had sensitisation to HDMs (positive specific IgE towards *D. pteronyssinus*), the median carpet dust concentration was significantly higher than in the homes of children without HDMs sensitisation. Exposure to HDMs allergen concentration level of $> 2 \mu\text{g/gm}$ was found to have higher serum-specific IgE to HDMs as compared with low HDMs exposure [31]. As mentioned earlier, the correlation of allergen exposure with sensitisation is a bell-shaped dose response which did not follow the linear pattern [19–21]. However, the mechanism of this response remains unclear and not well described.

Environmental factor plays a major role in HDMs survival and reproduction. High levels of HDMs allergens were found in old homes and damp homes [32]. It demonstrates that humidity is a crucial factor to determine the concentration of HDMs. It also explains the high prevalence of HDMs sensitisation in tropical countries with equatorial climate (hot and humid throughout the year) with an average humidity of more than 75%. Conversely, high level of HDMs is not found in high altitude area [33]. High level of HDMs is commonly found in mattress, sofa, and carpets [22, 32]. The age of the mattress determines the concentration of HDMs as high level of HDMs is found in old mattress [32].

The individual tendency in developing HDMs sensitisation is the similar environmental exposure of HDMs concentration with others are explained by the role of genetic factors and familial tendency. Any children are at high risk of developing AR when their parents have AR with the influence of their mother greater than their father [34]. However, the complex mechanisms of inheritance and genetic predisposition are not well understood and not well described. In recent years, many genome-wide studies were conducted to determine the association of allergic diseases with genetic susceptibility. However, there are still limited data on genome-wide association studies in AR as compared with asthma. The

genes that are associated with AR are different according to the ethnicities and populations. The genes found associated with AR in Caucasians is C11orf30/LRRC32 located at chromosome 11q13 [35•] whereas in Chinese population, it is rs4982958 located at chromosome 14q11.2. However, their association with HDMs sensitisation was not clear [36]. The replication of genome-wide association study for AR and HDMs found the genes associated with HDM sensitisation are rs2155219, rs7617456, and rs1898671, of which only rs2155219 is significantly associated with AR [37]. There might be genetic variability of different population towards allergens which affects their response and severity of disease. Further studies are warranted to identify and confirm such variability.

Infections, particularly viral infections, have influence in the development of immune system. This is supported by 'hygiene hypothesis' which stated that the microbial stimulates Th1 response that can counterbalance allergen-induced Th2 response [38, 39]. A study among farmers and agricultural industry workers found that the prevalence of AR in adult declines with increasing occupational endotoxin exposure [40]. Early exposure and contact to animal houses before the age of 7 years old is found to be inversely related to atopy [41]. This leads to the belief that reduced exposure to microbial increases the risk of developing sensitisation and allergic diseases later in life.

Pharmacotherapy

Administration by oral route

Anti-histamines are the mainstay of the treatment for allergic disorders. These agents are useful for treating the itching due to the release of histamine in both children and adults. Three generations of anti-histamines are currently available: the sedating first-generation anti-histamines such as chlorpheniramine, the non-sedating second- and newer-generation agents such as loratadine and desloratadine, respectively. The main concerns of first-generation anti-histamines are their sedative effects and interference with rapid eye movement sleep. The second and newer H₁ anti-histamines have minimal sedative properties due to minimal penetration of the central nervous system, minimal anti-serotonin, anti-cholinergic, and α -adrenergic blocking activity [42]. Vuurman et al. [43] conducted a study on 52 children with a history of seasonal AR. They found that children who were treated with the second-generation anti-histamine showed significant improvement in nasal symptoms scores ($P < 0.01$) than did children with AR who were treated with the first-generation agent.

Cromoglycate is a mast cell stabiliser, such as cromolyn sodium, which can be useful in relieving nasal pruritus, rhinorrhea, sneezing, and obstruction by preventing the release of histamine from mast cells. However, it has a compliance issue due to its short duration of action. Lejeune et al. conducted a study on patients with HDMs sensitisation and presented with mild to moderate AR. They found that patients who received sodium cromoglycate showed significant improvement of all symptoms (nasal obstruction, sneezing, and rhinorrhea) compared with placebo [44].

Leukotriene receptor antagonists such as montelukast and zafirlukast have been documented to have clinical benefit in patients with asthma. They have a role in relieving nasal obstruction and ocular symptoms due to inhibition of the late-phase allergic reaction [45, 46]. Meltzer et al. in 2000 found that a combination of anti-leukotriene and anti-histamine showed a significant reduction of

nasal and ocular symptoms compared with montelukast monotherapy [47]. Study by Pullerits et al. found no significant difference in reduction of epithelial eosinophil counts in patients treated with a combination of montelukast-loratadine compared with placebo. Further research is essential to study the role of leukotriene antagonists in patient with allergic rhinitis [48].

Administration by intranasal route

A systematic review on the randomised control trials showed that intranasal corticosteroids produce greater relief of AR symptoms that includes nasal obstruction, rhinorrhea, itching, sneezing, and postnasal drip [49, 50]. However, there is no improvement in nasal discomfort and nasal resistance. Corticosteroids prevent the release of cytokines resulting in inhibition of IgE-mediated release of mast cell-derived mediators causing reduction of circulatory levels of proinflammatory cells [51–53]. Pullerits et al. conducted a double-blinded, randomised study on 62 patients with grass pollen-induced AR. They found that intranasal corticosteroids therapy was more effective than the combination of anti-leukotriene and anti-histamine in reducing pollen-induced AR [48]. Intranasal corticosteroids cause far less side effects over those of oral corticosteroids. There are concerns about the potential growth retardation, hypothalamic-pituitary-adrenal suppression, and behavioural disturbances of systemic corticosteroids. However, the intranasal corticosteroids act locally on the nasal mucosa and are not associated with the same side effects as the systemic agents, and do not produce clinically significant side effects [54, 55].

Intranasal decongestants cause local vasoconstriction within the nasal mucosa through α -adrenergic agonists thus effective in reducing the symptoms of nasal congestion. However, decongestants have no effect on rhinorrhea, sneezing, and itching [56, 57]. A combination with anti-histamines may be effective to reduce those symptoms. It is important to note, however, that intranasal decongestants can give rise to rebound congestion and should not be used for more than 7 days. Oral decongestants are not recommended for children due to their cardiovascular side effects [40, 56, 57].

Intranasal anti-cholinergics such as ipratropium bromide act by reducing secretion induced by parasympathetic stimulation. It has significant effect in improving rhinorrhea in both children and adults [57].

Administration by injection route

Various interleukins suppress the allergic inflammatory process pathway and implicate the pathophysiology of allergic diseases. Long-term laboratory and clinical studies are currently in progress to find out the effect of anti-interleukins (anti-IL-5, anti-IL-4 and anti-IL-13) in patients with severe atopy [58]. Anti-IgE such as omalizumab is a recombinant humanised monoclonal antibody. It acts by blocking the interaction between free IgE with mast cells and basophils, therefore the free IgE level is reduced in the circulation [59].

Preventive strategies

Preventive strategies have gained acceptance for the management scheme in the treatment of patients with allergic rhinitis. Preventive measures

include allergen avoidance, environmental control, and immunotherapy. In all cases, the primary goal of treatment is to reduce the burden of disease, improve quality of life, and to prevent the development of the sequelae of AR such as bronchial asthma.

Avoidance of allergen

Preventive measures include increasing awareness of the sensitive individual about avoiding exposure to allergens is an important therapy of the treatment of AR. There is a correlation between the amount of exposure and the degree of sensitisation. Thus, exposure to HDM allergens should be minimised in susceptible children as much as is feasible. Parents should be educated about the essential of allergen avoidance measures and advised to implement them to the extent possible. When pollen counts are high, patients with seasonal AR may stay in the house with bedroom windows and doors close and use air conditioning on an indoor cycle with filters. Other measures are control timing of outdoor exposure, vacationing near pollen-free areas such as beaches, restrict camping, hiking, raking leaves, drive in air-conditioned car, use portable high-efficiency particulate air filter systems and electronic precipitators at home and in the car, avoid fresh-cut grass, do not mow lawn and shower after outdoor activities to remove pollen, and avoid contamination bedding.

For those with perennial AR, they are advised to reduce indoor humidity to less than 50%, avoid exposure to animal dander by removing furred pets from the home, remove wall-to-wall carpeting, wash bed linen in hot water, remove curtains from bedroom windows or wash frequently, use allergen-proof casings for mattress, box spring and pillows, replace feather comforters and pillows with cotton or synthetic materials, remove upholstered furniture, and check the house for standing water and mould [60, 61]. Contamination of food by HDMs should be avoided as such possibility is high in HDMs infested house hold where raw food is not properly stored. It is important to store food such as flour in sealed dust mite-impermeable bags, ideally in the freezer or refrigerator.

Immunotherapy

Allergen immunotherapy or hyposensitisation to specific IgE antibodies to clinically relevant allergens is one of the preventive treatment options for children with AR, asthma, and eczema, which often coincide. It acts by modulating the immune system activity by inducing desensitisation through gradually increasing the dose over period of time [60]. The strategy is to inhibit the development of sensitisation and it should be considered if other measures failed to sufficiently control AR symptoms. The preventive treatment using allergen immunotherapy depends on several factors including severity of the symptoms, benefit of optimum pharmacotherapy, any side effect of medication, and patient preference such as to avoid long-term pharmacotherapy [61].

Besides being used in prevention, allergen immunotherapy (AIT) is also used as one of the treatment options of HDM-AR. Immunotherapy

has proven its efficacy in multiple randomised control trials (RCT). Its treatment in AR has made it less likely for the subsequent progression into asthma [62••, 63–66]. Although AIT is effective in treating HDM-AR, it is costly and not without any complications. One of the most feared complications is systemic allergic reactions (0.2% risk per injection) and even life-threatening anaphylaxis requiring epinephrine administration especially with subcutaneous immunotherapy (SCIT) [8•]. Compared with SCIT, sublingual immunotherapy (SLIT) has an improved safety profile [8•]. SLIT has shown to induce long-term remission after discontinuation and may prevent new sensitisation [62••]. The clinical effect of SLIT is at least for 1 to 2 years after treatment discontinuation. Canonica et al. [67] after reviewing 77 double-blinded, non-randomised, placebo-controlled trials of SLIT concluded that SLIT was clinically effective in treating patients with rhinoconjunctivitis and asthma. In terms of safety, SLIT is well tolerated, has less systemic reaction (mainly at induction phase), and without any reported fatality or SLIT-related systemic hypotension. SLIT appears to be associated with less severe and fewer side effects as compared with SCIT. Due to its greater safety, administration of SLIT can be performed in outpatient clinic which is more convenient for patients [63].

The main indications for SLIT administration [62••] are patients with history of symptoms related to allergen exposure with positive SPT/specific IgE test, patients with uncontrolled allergy with optimal pharmacotherapy, pharmacotherapy induces undesirable side effects, and patients who do not want to be on constant or long-term pharmacotherapy.

Environmental control

Decreasing exposure to HDMs requires a combined approach that addresses facilitative factors, sources, and exposures to susceptible individuals. A government policy on environmental control to decrease HDM population is crucial. As there is synergistic effect of pollutants on HDM-AR, a better environment control of vehicles using carbon fuel should be tightly regulated, whereby the use of electric car should be recommended. The use of electric car which uses less carbon fuel will help reduce pollutants.

The use of HEPA filtration can decrease local exposure to airborne mite allergens and to some irritants in public place and home [68••]. HEPA cleaners should be placed in areas of mite contamination where air disturbance is likely to suspend particles so that they are available for removal. Their use can be encouraged and even promoted if government can provide incentives such as tax free or deductible expense from income tax. The humidity monitoring in old building is essential to reduce the load factor of HDMs as old building has high load of HDMs [68••]. Regular home assessment for HDMs and humidity analysis will help to reduce exposure.

Conclusions

Prevention is a viable option and key component in HDM-AR management. As urbanisation and lifestyle changes lead to the increase of HDM-AR, there should be a more concerted effort towards prevention. Considering the burden of

disease and economic impact, allergy programs in the form of better education, and prevention will help promote better airway health.

Compliance with Ethical Standards

Conflict of Interest

Salina Husain declares that she has no conflict of interest. Farah Dayana Zahedi declares that she has no conflict of interest. Sakinah Mohamad declares that she has no conflict of interest. Baharudin Abdullah declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- A very good article on practice parameter for house dust mite-induced allergic rhinitis prevention.

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