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Abstract

When we are considering the source and production of antigenic and allergenic particles, proteins and toxins, and exposure to them, the indoor environment can be more complex than the outdoor. These bioaerosols and biopollutants may include microbial cells, their reproductive units and metabolites that are small or volatile enough to achieve aerial dissemination. Among these the sensitizing or allergenic agents which are generally >3-20 mm in diameter may play an important role in bronchial asthma.

Concentrations of house dust mites, Dermatophagoides pteronyssinus (Der p I - Der p II), D farinae (Der f I and Der f II) as well as material originating from household pets, eg cat saliva and dander (Fel d I), cockroach faecal particles (Per a I), and a number of fungal spores, particularly Alternaria (Alt a I) and Aspergillus (Asp f I) species, can contribute to the development of bronchial asthma in both children and adults. The impact of the indoor environment on human health constitutes a serious health risk and needs more attention to both short- and long-term health effects. Indoor environmental factors, particularly house dust mite and other allergens of pet origin, are very common in sensitization and the development of bronchial asthma in Saudi Arabia.

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REVIEW

Indoor environment and house dust mites:
risk factors in bronchial asthma

Introduction

Exposure to indoor allergens in susceptible individuals may lead to sensitization (development of specific IgE antibodies) and/or elicitation of allergic symptoms in already sensitized subjects[1]. Allergic symptoms caused by allergens of indoor origin include bronchial asthma, allergic rhinitis, atopic dermatitis and conjunctivitis, as well as bronchopulmonary aspergillosis and hypersensitivity pneumonitis (extrinsic allergic alveolitis)[2,3].

Indoor allergens comprise a very potent group of allergens and are considered to be responsible for most cases of perennial symptoms of allergic rhinitis and extrinsic asthma. Indoor allergens originate mainly from indoor sources, but outdoor (including back yard or garden) sources such as plants and grasses can contribute to the allergen concentration of the indoor environment[4]. Such indoor allergens and biopollutants come from a number of sources both within the home and from outside. Indoor allergens which are known to be widely prevalent in many parts of the world come from both the animal and plant kingdoms[5-10].

Two very potent and well-known allergens (out of 50 000 species of mites in the world environment) are the house dust mites (HDMs) *Dermatophagoides pteronyssinus* (*Der p* 1-7) and *D farinae* (*Der f* 1-5) (family Arachnidae)[11]. Other HDMs present in house dust and known to be allergenic are *Euroglyphus maynei* (*Eur m* 1), *Blomia tropicalis* (*Blo t* 5) and *Lepidoglyphus destructor* (*Lep d* 1).

Animal (mammal) allergens

mainly include *Felis domesticus* (*Fel d* 1), *Canis familiaris* (*Can f* 1), *Mus musculus* (*Mus m* 1) and *Rattus norvegicus* (*Rat n* 1).

Two well-known cockroaches have been found to be allergenic. These are *Blatella germanica* (*Bla g* 1-5) and *Periplaneta americana* (*Per a* 1 & 3) from the family Blattidae; approximately 1% of the 3500 members of this family of orthopterous insects are domiciliary pests[11]. *Blatta orientalis*, *Periplaneta australasiae* and *Supella supelledium* are also known to be present in homes but reports of allergenicity to these species are not available.

House dust mite is a mixture of various components and may include harmful substances originating from sources within the home as well as those brought from outside. HDMs are tiny creatures and are known to be one of the most prevalent and significant components of house dust in areas where sufficient humidity (>50%) remains available[27,28]. These mites do not usually flourish in dry conditions or areas where relative humidity is less than 50%[29,30]. The two most prevalent HDMs incriminated in causing allergic reactions are *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* and, to a lesser extent, *Dermatophagoides microceras*, all members of the family Pyroglyphidae.

Immediate-type hypersensitivity reactions (Type I or IgE-mediated) to the above two species of HDM are common and manifestations include bronchial asthma, conjunctival allergy, allergic rhinitis, atopic dermatitis and urticaria. Patients allergic to mite frequently have IgE antibodies to a wide range of mite antigens[31,32] with a considerable heterogenicity between individuals in the spectra of these responses.

The importance of HDM allergy was established in 1967 and subsequently evidence for sensitization of patients with asthma to HDM allergens has been reported from many different parts of the world[33]. Since 1967, many different mite allergens have also been identified and purified.

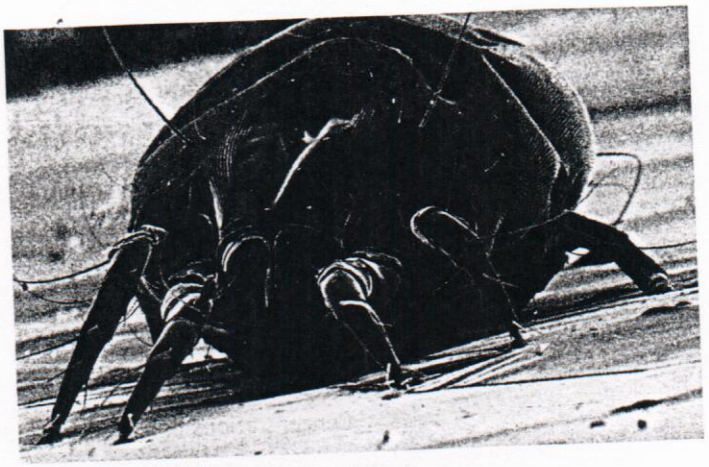

Figure 1: House dust mite

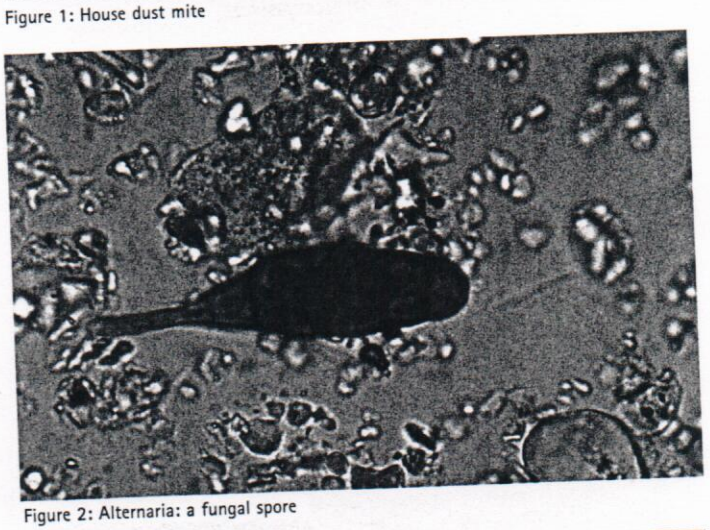

Figure 2: Alternaria: a fungal spore

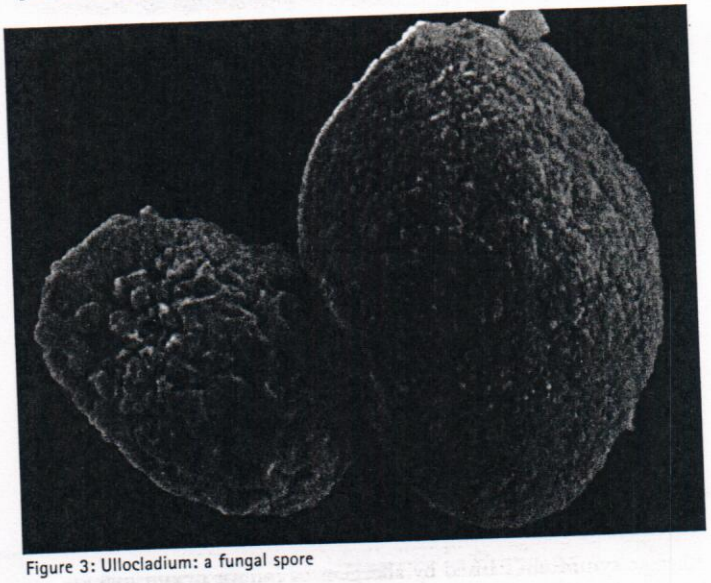

Figure 3: Ullocladium: a fungal spore

Many mite species eat fungi, and there is some evidence that the pyroglyphid mites are dependent on fungi either for the digestion of skin scales or perhaps as a growth factor. It is thus not surprising that conditions for mite growth are similar to those for fungi. Reduction in humidity will generally reduce the growth of both fungi and mites. However, fungi can grow on open surfaces and at temperatures in which mites will not flourish.

Thus a basement without carpets can produce a large number of moulds but is unlikely to have large numbers of mites. Levels of

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mite allergens are usually low in undisturbed rooms and fall rapidly after disturbance. Air filtration can have a small role if the allergen is airborne for only a short time and is present on the floor in enormous quantities[25].

Indoor allergens also include allergens of plant origin. These include various fungi originating from different indoor sources such as assorted fruits and vegetables (eg onion, garlic, ginger[13]). Stored and discarded jam, jelly, cheese and bread can also be potent sources of fungal growth.

Fungi which are found indoors are usually from the "mould group" commonly called "mould and mildews"[14]. Airborne pollen grains from nearby outdoor sources can enter the indoor environment. Basidiospores from the mushroom fungi growing in the backyard in wet and humid regions[15] and ascospores such as Leptosphaeria spp (the pefect state of some phoma spp[16]) can enter the indoor environment with the air currents through open doors and windows. Allergenicity to basidiospores has been established and allergenic extracts of some basidiospores are now commercially available[17].

Standardization

For accurate diagnosis and safe immunotherapy involving indoor aeroallergens an understanding of the importance of allergenic extracts and their standardization is very important. Classical standardization of allergenic extracts on the basis of "protein content" or "weight per volume" do not correlate with the "allergenic activity" and "biological potency" of the extracts. However, there have been advances in allergen characterization and standardization by mAb ELISA and cDNA sequencing by molecular technique and now, from Protein Nitrogen Unit (PNU), Weight per Volume (W/V), and Allergy Unit (AU/ml), it has been possible to acquire allergen extract in FDA-approved Bioequivalent Allergy Units (BAU/ml). At present this is limited to cat and dust mites.

Careful selection of allergen extracts in countries like Saudi Arabia will provide better clues for precise diagnosis and successful immunotherapy for IgE-mediated allergic diseases, particularly in asthmatic patients. Quality of extract is very important because this may alter the overall diagnostic pattern, allowing for more accurate diagnosis and fewer false negatives.

Allergenic fractions

During the past 10 years, different mite allergens have been identified. Some of these have been purified and monoclonal antibodies (mAbs) have been developed against the purified allergens. An International Standard (IS) for *D pteronyssinus* has also been adopted by the World Health Organization with Code 82/518 NIBSC (National Institute for Biological Standard and Control[1,25]).

Major allergenic components are known to be proteins and glycoproteins of molecular weight 10-50 kd which are mostly contained in faecal particles (HDMs and cockroach), saliva (cat, rat), urine (rat and mouse) and spores (fungi). Household items such as carpets, mattresses, pillows, furniture, stuffing, bedding, fur, clothing and leather are known to contain most of these allergens, while the airborne concentration of the allergen particles can reach their peak with indoor human activities such as dusting, bedmaking and vacuuming[12].

Two major groups of allergens have been defined from the genus *Dermatophagoides*. The group I allergens (*Der p* 1, *Der f* 1 and *Der m* 1) (where the former stands for genus and the latter for species) are 24 000 molecular weight (M/W) glycoproteins, heat labile and heterogenous on isoelectric focusing (isoelectric point-p1) (4.7-7.4 p1)[11]. These allergens are excreted in faeces and appear to be structural homologues and have very similar N terminal amino acid sequences.

The group II allergens (*Der p* II, II) are 15 000 M/W proteins. The gene-inducing *Der p* 1 has also been cloned and the full amino acid sequence has been deduced from the cDNA[11].

Cross-reactivity within the group (or group II allergens) has been noted but there is no evidence for cross-reactivity between group I and group II allergens. Some laboratories have produced mouse-derived MAbs to group I and group II allergens and these have been used for allergen purification, epitope mapping studies and developing specific immunoassays for allergen quantification. Assays of allergens should be related to an established national or preferably IS extract[11].

International Standards

The best established and characterized extract available at the moment is the WHO International Standard (IS) freeze-dried glass (NIBSC Code 82/518). This standard was assigned a potency of 100 000 IU. The ampoules contain 12.5 µg of *Der p* 1 and 0.4 µg of *Der p* II. The FDA in the United States has also produced its own mites standard[11].

NIBSC (Code 82/528) ampoules are considered to contain 1150 units of IgE antibody to *D pteronyssinus* and recent studies indicate that this unit is approximately 0.1 ng of IgE antibody. Thus it has been suggested that 40 RAST units (ie 5 ng/ml) should be regarded as a definite positive and 200 RAST units (ie 20 ng of IgE antibody/ml) should be regarded as a high level. The FDA standard for *D pteronyssinus* contains 46 µg of *Der p* 1 and about 25 µg of *Der p* II/ml of extract. The FDA *D farinae* standard contains 35 µg of *Der p* 1 and approximately 16 µg of *Der p* II/ml of extract.

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Recently, efforts have also been made to explore the antigenic and allergenic relationship between the house dust mite *Dermatophagoides pteronyssinus* and three species of storage mites, ie *Lepidoglyphus domesticus*, *Acarus siro* and *Tyrophagus lonior*. Cross-immuno-electrophoresis demonstrated that all the mite extracts contained multiple antigens but that there was only limited cross-reactivity between the different species.

Threshold level

Estimation of the allergenic threshold or critical level is calculated in microgram (µg) or nanogram (ng) quantities (1 µg =1000 ng) of highly purified allergens of HDM species. Thus the specific allergen threshold for an acute attack of asthma or a level at which most sensitive patients will experience symptoms is considered to be 2 µg *Der p* 1 per g of dust, which is equivalent to 100 mites/g (or 0.61 µg guanine/g) of dust. A level below this may effectively reduce the symptoms.

As individuals vary enormously in their sensitivity, there have been comments that the proposed standards may not be applicable to all allergic patients. However, any approach to analyse or evaluate the critical level (or effective reduction) of mite allergens should be based on the following criteria[1,25,26]:

- the level of exposure that is a risk for inducing sensitization
- the level in homes that is a risk for increasing the prevalence of symptomatic asthma in a community
- the level in homes that is a risk for an acute or severe attack of asthma among individuals allergic to mites
- the quantitative reduction in exposure to mite allergen which is necessary to produce a significant clinical improvement.

Skin prick test

Skin prick testing (SPT) and measurement of IgE antibodies with the radioallergosorbent test (RAST) are generally used for determining HDM sensitization. In SPT, an extract containing 20-70 µg of *Der p* I /ml correlates with serum assays for IgE antibody and can be consistently reproduced on repeat SPT with mite extract of similar potency.

In Saudi Arabia

In Saudi Arabia, studies were conducted to establish the prevalence[18] and possible contribution of allergens of indoor origin in the aetiology of allergic diseases, particularly bronchial asthma[19-21]. Studies in various regions of Saudi Arabia have confirmed the presence of indoor allergens with considerably qualitative and quantitative diversity[22-24].

The geographical centres included in our studies are Riyadh and Gassim (Central Region), Jeddah (Western Region) and Abha (Southern Region). Indoor allergens identified from the above regions were *Der p* 1, *Der f* 1, *Fel d* 1 and *Per a* 1, as well as various spores.

Significant diversity was recorded in the composition of *Der p* 1, which is prevalent in the Southern Region, and *Der f*, which is prevalent in the Western Region. Riyadh (Central Region), which has a low humidity, did not show any significant amount of any HDMs in dust samples. In contrast, *Per a* 1 was more prevalent in Riyadh.

As mentioned above, the clinical threshold or risk levels of *Dermatophagoides* spp have been proposed as 2 µg/g dust (approximately 200 mites) of *Der p* or *Der f* Group I as the sensitization level and 10 µg/g dust (approximately 500 mites) for causing severe attacks of bronchial asthma[1,25]. Not only were these levels detected in Saudi homes, but in addition the risk levels were exceeded in parts of the Kingdom[24].

Conclusion

HDMs are humidity-dependent and long periods of dry weather are not favourable to mite species. Since Riyadh has low relative humidity while Jeddah has the highest for most of the year, the variation in dust mite content is basically attributable to variation in humidity level.

On this basis it can be expected that various regions in Saudi Arabia will have different levels of HDMs. No previous data on HDMs from Saudi Arabia appear to be available. Nevertheless, a number of patients in Riyadh also react positively in SPT to glycerinated HDM extracts, indicating their sensitization to HDM species.

These sensitized individuals are at risk and although they may develop symptoms on second or subsequent exposure, it is likely that these patients were either exposed to HDM in other areas of the Kingdom or abroad. However, it is possible that the relative indoor humidity in many Riyadh homes is maintained by the abundant use of house-plants or by using humidifiers which favour the growth of HDMs.

In Jedddah and Makkah regions, a higher percentage of patients reacted positively to HDM extracts in SPT. This, combined with the high humidity in the regions and dust analysis results revealing HDM levels many time higher than the critical level, indicate that allergic manifestations, including bronchial asthma in many patients, may have been caused by HDM allergens.

More environmental studies in various parts of Saudi Arabia, as well as further *in vivo* and *in vitro* studies, need to be conducted in order to investigate the possible regional variations and quantitative level of these HDMs; and the species involved, as well

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as their possible role as extrinsic allergic factors in the sensitization and elicitation of perennial symptoms in Saudi Arabia.

Apart from HDMs, cat allergen (*Fel d* 1) and cockroach allergens (*Per a* 1) appear to be the other two major indoor contributors to bronchial asthma. Both *Fel d* 1 and *Per a* 1 have been reported to be allergenic and prevalent in many parts of the world[34-42]. Frequency, shared antigens and cross-reactivities between the allergens of HDMs, *Fel d* 1and *Per a* 1 also need further investigations in the Kingdom.

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Your Questions Answered

Question

When do the clinical signs of rickets disappear after the child has received full treatment?

Answer

The commonest form of rickets is the nutritional rickets caused by vitamin D-deficiency. In infancy the clinical manifestations include:

- craniotabes
- delayed closure of anterior fontanelle
- rachitic rosary
- Harrison's sulcus.

Later in childhood the signs include:

- enlargement of epiphyses at wrist, knees and ankles
- bowing of legs.

With adequate treatment, which should include vitamin D supplementation, adequate calcium intake, education in nutrition and child care, as well as modest exposure to sunlight, reports suggest that it possible to achieve clinical cure within months in most patients with nutritional and even vitamin D-dependent rickets[1,2].

The disappearance of clinical signs will depend on the time of presentation and the severity of the disease. In children who are diagnosed early, the clinical changes usually resolve wihtin 12 months[1,2]. In older children and especially those with severe limb deformities, clinical improvement may take up to a few years[2,3]. In patients with long-standing disease and severe deformities, surgery may be required to correct physical anomalies and even then, final correction may not be perfect[2].

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We invite you to send in your questions on paediatrics to our panel of experts. We regret we can only answer those questions that are selected for publication, and our experts cannot enter into individual correspondence.

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