

Exposure to Dog Allergens and Subsequent Allergic Sensitization: An Updated Review

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Abstract Dog exposure and development or exacerbation of allergic disease and asthma remains an important topic of research. The emotional connection between humans and pets can be quite influential in decisions about removing a pet from the home for health reasons. Patients also often ask about “hypoallergenic” dog breeds or treatments to make their dog less allergenic. Research has examined the link between early life exposure (prenatal, perinatal, childhood) to dogs and an apparent reduced risk of developing allergies later in life, but no consensus has emerged to assist patients or physicians. An important question is whether there are certain ages or conditions under which living with a dog may increase or decrease the risk of allergic sensitization. A better understanding of the variables influencing the outcome of in-home dog exposure will hopefully make significant advances toward alleviating the symptoms associated with allergic sensitization to dogs.

Keywords Dog · Can f 1 · Asthma · IgE · Sensitization · Age-related exposure · Microbiome · Hypoallergenic · Socioeconomic · Toxocara · Sublingual · Immunotherapy · Allergens · Treatment

Introduction

The development of allergic symptoms and asthma-related to exposure to dogs still presents a significant problem for

dog lovers and allergists alike. According to the American Pet Products Association 2011–2012 National Pet Owners Survey, there are approximately 78.2 million dogs owned in the United States alone, making them the third most populous pet behind freshwater fish and cats. Approximately 39 % of all US households include a dog, with 40 % of those households having 2 or more dogs. Levels of the primary dog allergen, Can f 1, have been found to be up to 50 times higher in homes where dogs are kept indoors [1•]. For those households where dogs are kept outdoors, or which do not include a dog, the problem remains relevant as studies consistently demonstrate dog and cat allergens in dust samples from up to 90 % of U.S. homes [1•, 2–6, 7••, 8, 9]. Additionally, pet allergen has been found in areas in which dogs are not usually found, including school classrooms [10•]. In the face of the increasing prevalence of allergies and asthma in the U.S. population, the high level of indoor dog exposure continues to be an important health concern. In 2010, it was estimated that individuals with known asthma who are allergic to pet allergens but continue to live with pets result in an additional 0.25 to 0.5 billion dollars in annual healthcare costs [1•].

In response to allergic animal lovers, dog breeders have continued to market the benefits of “hypoallergenic” dogs to the public. The popularity of “hypoallergenic” dogs continued to increase with the presidential purchase of a Portuguese water dog, purported to have less shedding and allergenicity. Some breeding companies have gone so far as to specifically breed dogs stated to have a lower amount of Can f 1. Companies such as Allerca Lifestyle Pets currently sell these dogs for a starting price of almost U.S.\$16,000 (www.allerca.com). Given that at least 5 separate dog allergens have been elucidated, some of which are not produced in dog dander, it is questionable as to whether a truly allergen free canine presently is available for allergic individuals desiring a dog [10•, 11••].

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Studies based on the hygiene hypothesis have investigated the relationship of early life exposure to dogs and other animals, and the development of asthma and allergic sensitization later in life [12]. A meta-analysis of 9 studies from 1995 to 2003 demonstrated an increased risk of asthma with early life exposure to dogs [12]. However, more recent birth cohort studies have shown a potential protective effect of dog ownership in the prenatal and perinatal periods, as well as the first year of life [5, 6, 7•, 9, 13, 14•]. The observation of protection against allergic disease in some studies has raised the question of a potential biological mechanism. Hypotheses have included exposure to higher levels of endotoxin in homes with dogs, tolerance from exposure to high levels of dog allergens, alterations in home microbial communities related to the presence of a dog, and possibly increased physical activity related to dog ownership. These studies raise the question of whether the timing of dog exposure in relationship to a person's age shift the outcome of exposure between decreased and increased risk of developing allergic sensitization. Also important in such research is the question of whether the results of dog exposure specifically influence only the risks of dog allergy or the risks of allergy to multiple allergens.

In this review, we provide an update on the research into dog exposure and the development and exacerbation of allergic sensitization, disease, and asthma. We discuss the various dog allergens and how they relate to the burden of illness associated with environmental allergens. We examine the relationships of family demographics to dog ownership and allergic sensitization, and review recent research into childhood exposure to dogs and the protective role it may play in later development of allergic symptoms. Finally, we review newly proposed treatments being evaluated to reduce or eliminate the symptoms of allergy stemming from sensitization to dog allergen.

Known Dog Allergens

Five dog allergens have dominated investigations of dog exposure and health. *Canis familiaris* 1 (Can f 1) is a lipocalin protein produced in the salivary glands of dogs and binds IgE antibodies in as much as 50 % of subjects sensitized to dog dander. [10•, 11••]. Its deposition on dander and house dust particles has been evaluated for its harmful and/or protective benefits on patients [4, 10•, 11••]. It has been demonstrated that homes where dogs are kept exclusively indoors have elevated levels of Can f 1 compared with homes where dogs are kept outdoors [4]. Moreover, owning a dog, in or outdoor, increases the levels in comparison to not owning a dog. However, even homes without dogs commonly display detectable levels of Can f 1 in dust samples [1•, 2–6, 7•, 8, 9]. While dog bathing has been

demonstrated to decrease overall dander and may reduce Can f 1 production, the effect achieved and the multiple washings per week required may be difficult to maintain [10•]. Multivariable models have suggested that neutering or spaying a dog results in increased Can f 1 levels in the home, though this finding requires further evaluation [4]. Most “hypoallergenic” dogs are advertised as such because they either shed less hair or have been bred to produce decreased amounts of Can f 1 in their dander. Decreased shedding does not eliminate exposure from dog saliva, however. Nor does it take into account the additional minor allergens that may still play a role in allergic symptoms.

Can f 2 is also a lipocalin protein found in dander and saliva [10•, 11••]. Can f 3 is derived from canine serum albumin, though the clinical relevance of serum albumin and allergen sensitization remains uncertain [11••]. Can f 4 is found in saliva, though its properties have yet to be fully defined. All of these represent minor allergens, producing a positive skin test response in less than 50 % of atopic patients [10•].

Focus has recently shifted to Can f 5, found in urine. Though the discovery of allergens in mammalian urine is not a new finding, early studies of dog allergens purported that there was minimal significant allergenic activity in dog urine. An IgE antibody-binding protein has since been isolated from dog urine [11••]. Can f 5 is a prostatic kallikrein that has been found in the urine and dander of adult male dogs. It has demonstrated significant IgE antibody binding activity in as much as 70 % of a study population with 30 % of that same population demonstrating IgE activity only to Can f 5 [10•, 11••]. Additionally, this allergen has been investigated for its potential role in cross-sensitization to human prostate specific antigen, leading to allergic vaginal reactions to human semen.

Can f 1 remains the predominant major allergen in epidemiologic research because of the availability of assays to measure its concentration in various types of samples. However, future research may shift to the other dog allergens and potential environmental changes to reduce patient exposure to them.

Associated Risk Factors

Studies continue to investigate relationships between patient characteristics and their choice of having a dog in the home, as well as the development of asthma and atopy. Socioeconomic status has been evaluated in multiple studies, though results are conflicting [15, 16•]. A 2010 study found an increased risk of atopy and greater skin prick positivity to common aeroallergens associated with higher paternal education and higher socioeconomic status [15]. A significant relationship between socioeconomic status and future

asthma diagnosis was not found. A recent study suggests a relationship between more pet ownership in homes of smoking parents [16•]. This finding and other demographic features including race, gender, geographic location, socioeconomic status, and family size still require significant research to more fully understand the conflicting results of current studies [15, 16•, 17].

Some researchers attribute a higher amount of allergic sensitization in homes without pets to a selective avoidance bias, in which families that have known histories or current diagnoses of atopy or asthma avoid acquiring a dog or remove the dog from the home to alleviate symptoms [15]. Studies have provided contrasting evidence for this theory [15, 16•]. One study found that the strongest predictor for never having a pet included allergic rhinoconjunctivitis in a child, but also showed that a diagnosis of asthma in a child did not influence acquisition or removal of a pet across all socioeconomic classes [16•].

While the inconsistencies of the literature concerning patient demographics and pet ownership remains important, investigation into potential infections from dogs is also gaining increased attention. Specifically, the potential effects of *Toxocara* infection on reduced lung function have been investigated for over a decade [18–21]. While it has been theorized that parasitic infections may assist in the prevention of IgE-mediated allergic disease via blockade of effector-cell receptors, murine models have suggested that the opposite may be true, resulting in atopic mediating potential [19, 21]. One of the first reports to describe an association between *Toxocara* infection and reduced FEV1 in a nationally representative population was completed in 2011 [19]. While the study indicated an increased risk of parasitic infection in men, immigrants, and those living in rural areas, even after controlling for many of the demographic facets previously discussed, the study still demonstrated a small but statistically significant decrease in FEV1 in patients who are antibody positive to *Toxocara*. Given the increased promotion of Th2 immune responses with helminth infections over Th1 responses, and their stimulation of very high levels of IgE production, this relationship is to be expected [19]. However, as the rate of immigration to the United States increases, the evaluation and treatment of previous or ongoing parasitic infection is likely to become more important as a source of increased atopy in the American population.

Age of Exposure

Though based on very limited studies, for many years it was assumed that exposure to either dogs or cats in infancy increased the risk that a child would become allergic to these animals in later life [2, 9, 12, 13]. However, more

recent prospective cohort studies have produced just the opposite conclusions. A 2010 systematic review of 13 birth cohort studies demonstrated that dog exposure during infancy and early childhood had no effect on the development of specific IgE reaction to dog allergens [5]. Additionally, significant conflict remains over whether or not dog ownership decreases the risk of developing asthma. Some cross-sectional studies have indicated that current dog ownership is associated with increased risk of asthma, while others demonstrate a decreased risk, and still other analyses show no relationship whatsoever [5]. However, there is support mounting for a protective relationship between dog ownership in early life and decreased development of sensitization to mixed aeroallergens, especially outdoor aeroallergens [5, 6, 9].

A possible reason for these conflicting conclusions related to dog exposure may be due to the specific period of time in immune development during which exposure to either dog allergens or other exposures coming from dogs may influence the development of asthma. Dog exposure at other ages may increase the risk of asthma. In 2010, Almqvist et al demonstrated decreased risk of sensitization to environmental allergens in patients with exposure to dog within the first 5 years of life [6]. Data also demonstrated that the presence of dogs before 5 years of age had no effect on the risk of current eczema, wheeze, or change in FEV1. From these results, at least a 5-year window of opportunity for exposure and protective benefits was proposed. That same year, a study of a high-risk birth cohort was carried out to evaluate the effects of exposure to a dog at various points during the first year of life upon the development of asthma and dog allergen sensitization at age 7 [22]. The intervention group required environmental control of house dust mite, avoidance of pets, and environmental tobacco antenatally and during the first year of life. The control group received no instructions on environmental alteration. In the control group, even if the family obtained a dog after the patient was older than one year, they still did not exhibit sensitization or asthma. However, in the intervention group with no dog exposure during the first year of life, the study showed a significantly increased risk of asthma by age 7 years.

Others have examined exposure to dog both antenatally and perinatally. In 2011, the Wayne County Health, Environment, Allergy, and Asthma Longitudinal Study (WHEALS) examined the trajectory of total IgE levels over the first 2 years of life in children whose mothers were exposed to dogs during their pregnancy [14]. The study demonstrated lower total IgE levels across the entire 2-year period when there was prenatal pet exposure. Interestingly, results showed a greater decrease in total IgE from dog exposure in children delivered by means of cesarean section vs vaginal delivery, a finding consistent with other studies [7•, 9]. The authors of this study suggest that the

lower total IgE levels are related to the greater bacterial diversity of house dust, which they previously demonstrated in homes containing dogs [7••].

Prenatal exposure serves as an easy marker for the earliest age of exposure to dogs and decreased sensitization. However, further efforts need to be made to determine the oldest age at which exposure would offer protection. A study by Wegienka et al. investigated the effects of exposure within the first year of life and at later ages on sensitization to dog measured at 18 years of age [7••]. Patients with indoor dog exposure in the first year of life had one-half the risk of dog sensitization at age 18 compared with those who did not have a dog during their first year of life. Interestingly, this effect was only found in male participants. Exposure to dogs at other ages did not appear to have any significant effect on the likelihood of sensitization. Likewise the cumulative life exposure was not related to sensitization if the individual was not exposed during the first year of life. The SIDRIA-2 study mirrored the results of exposure to dogs within the first year of life, showing no increased risk of development of respiratory or allergic symptoms [13]. This study also demonstrated no significant effect with exposure to dog after one year of age. However, evaluations were only conducted out to 7 years of age, whereas the study by Wegienka et al evaluated symptoms in patients up to 18 years old.

A 2012 systematic review of 9 longitudinal studies from 1998–2011 confirmed earlier studies findings of decreased total IgE with prenatal and perinatal dog exposure [9]. A lower risk of wheeze, asthma, and aeroallergen sensitization resulted from exposure at less than one year of age. Included in these studies was the Childhood Origins of Asthma Study (COAST), a birth cohort study of a high-risk population for atopy, which also demonstrated a lower risk of atopic dermatitis by 1 year and at 3 years in patients who were exposed to dogs at birth [9, 23]. In this high-risk group, it was shown that postnatal exposure to dogs might result in overall decreased allergic sensitization by enhancing IL10 and IL13 responses in the neonate.

In summary, the current studies suggest the period from approximately 20 weeks gestation to one year of age serves as a critical time during which exposure to dogs may result in protective effects against subsequent development of allergic symptoms [9]. Inconsistencies remain regarding which symptoms are most likely to be affected. Further research is required to investigate whether other variables influence the protective effect associated with dog exposure, including delivery by cesarean section and breastfeeding. Additionally, further analysis is needed to determine if the protective effect of exposure spans the entire first year of life, or if the window of potential protection is of a shorter duration, such as the first 6 months.

Treatment

Subcutaneous immunotherapy (SCIT) is often employed in the treatment of dog allergies. However, as of 2010, studies of dog SCIT demonstrated only modest results [3]. While skin prick sensitivity was reduced after therapy, some studies have shown no significant differences in allergen specific IgE or IgG and no change in bronchial challenge after 5 months of treatment [24•, 25]. One explanation for these findings is that the dog allergen extracts used in these studies were not standardized for specific allergen content according to guidelines established in the 2007 American Academy of Allergy, Asthma, and Immunology (AAAAI) Practice Parameters for Immunotherapy (www.aaaai.org). In the meantime, attempts at allergen avoidance and appropriate pharmacologic therapy remain the mainstays of treatment specifically for sensitization to dog allergens and subsequent asthma [3].

Studies have examined routes other than subcutaneous injection, such as intranasal administration or oral administration with sublingual immunotherapy (SLIT). Studies performed on SLIT have thus far shown it to be generally safe, though cases of nonfatal anaphylaxis have been reported [24•]. A meta-analysis of 49 randomized placebo controlled trials of SLIT has shown overall efficacy for the therapy [26]. However, most of these studies only investigated the effect on allergic rhinoconjunctivitis, and none of them specifically focused on dog allergens. Few studies have been performed to compare this efficacy to that achieved with SCIT. Additionally, optimal dosing regimens and duration of treatment have not been established. As more studies are performed, SLIT may continue to gain support. At this time, too many questions remain unanswered for both its use in multi-allergen therapy and canine allergen.

Conclusions

Conflicting evidence into the effects of exposure to dog allergens and the subsequent risk of developing allergic sensitization and asthma continues to present a challenge to researchers, physicians, and veterinarians. The bond between people and their canine counterparts remains a powerful motivation for in-home pets, even in the face of a history of allergic symptoms or ongoing exacerbations. However, researchers continue to make bold strides on multiple fronts. As we continue to identify the multiple canine allergens that are at play, we increase the opportunity to treat the patient for both major and minor allergens, rather than simply Can f 1. With further evaluation of the multifactorial causes for allergic sensitization to dogs, especially at the cellular level, we can develop a well-rounded therapeutic and pharmacologic approach to patient care. Multiple

birth cohorts provide us the opportunity to extend the search for a “window of opportunity” during which exposure to dogs will offer long-term protective effects, rather than causing an increase in sensitization. As new forms of immunotherapy and its administration are developed, the door to easier and, potentially, more efficacious treatment becomes a reality. Most importantly, with these continued efforts, we improve our knowledge base and the opportunity for patient education on the potential harms and overall joys that come with owning “man’s best friend.”

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