

Original Article

Prevalence of serum allergen-specific immunoglobulin E for canine atopic dermatitis in Korea

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Canine atopic dermatitis (CAD) is an allergic skin disease with characteristic clinical features associated with immunoglobulin E (IgE) antibodies. Identification of the causative allergens is the diagnostic goal, which is essential to treat and manage CAD patients. CAD is commonly associated with environmental allergens surrounding the patients. For this reason, it is important for diagnostic tests to select allergens that are related to the environment of each country and each province. There are two main allergen-specific tests, serological IgE test (SAT) and intradermal skin test (IDT). SAT did not show direct cutaneous reaction but did show serological reaction against allergens. However, SAT is simpler and more convenient than IDT in small animal practice. In this study, we selected domestically prevalent allergens for SAT, including 60 food allergens and 60 inhalant allergens, and tested eight dogs tentatively diagnosed with CAD based on Favrot's criteria. Furthermore, IDT was performed on four dogs from the SAT group for comparison of SAT and IDT, and the results were very similar. In SAT, four types of mites (*Bloomia tropicalis*, *Glycophagus domesticus*, *Euroglyphus maynei*, and mite mixture 1 Korea; house dust mites), four types of molds (*Botrytis cinerea*, *Alternaria alternata*, mold fungi mixture 11, mold fungi mixture), and one type of pollen (tree pollen mix 3 Korea) induced a reaction in more than half of dogs tested. In IDT, all four dogs reacted positively to *Dermatophagoides farinae*, and three reacted positively to *Dermatophagoides pteronyssinus* and house dust. The mean agreement rate between SAT and IDT in this study was 76.3%. This is the first trial to apply local allergens for SAT in Korean veterinary medicine, and it might play an important role for diagnoses and management of animal allergic diseases.

Key words: atopic dermatitis, serum allergen-specific IgE test, intradermal skin test, dog, Korea

Introduction

The definition of canine atopic dermatitis (CAD) is genetically predisposed inflammation and pruritic skin disease with characteristic clinical features associated with immunoglobulin E (IgE) antibodies most commonly directed against environmental allergens [1]. Since there is currently no definitive diagnostic test for CAD, veterinary diagnosis is based on the evaluation of clinical symptoms and the exclusion of other potential causes [2, 3, 4].

Once a tentative diagnosis of CAD is made based on clinical criteria, testing for allergen-specific IgE can help to confirm the diagnosis. The most common methods of allergen-specific testing in veterinary medicine are the intradermal skin test (IDT) and the serum allergen-specific IgE test (SAT). IDT is widely accepted as the gold-standard technique for allergic skin diseases [5]. Nonetheless, IDT is limited by the requirement for anesthesia, shaving, and the withdrawal of medication that may influence allergic reactions [5]. Consequently, SAT is used more frequently than IDT because of its convenience: only a small volume of animal serum is required for testing and withdrawal of anti-allergy drugs is not necessary [6]. It is essential to identify the specific environmental allergens in domestic region and residential area for allergen-specific IgE tests. Unfortunately, there is no commercially available SAT based on specific geographical allergens for dogs in Korea. In this study, 120 common allergens in Korea were designed for use in a

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canine SAT and applied to eight dogs with CAD. Four of them were also tested by IDT to compare the results between SAT and IDT.

Materials and Methods

Serum allergen-specific IgE test (SAT)

Eight dogs with dermatological problems were selected for testing in this study (Table 1). The dogs were tentatively diagnosed with CAD based on the two sets of diagnostic criteria proposed by Favrot *et al* (Table 2) [2].

Despite failing to meet the criteria, however, dog 3 did display the three key observations [5]. Exclusion of differential diagnoses for CAD signs and symptoms was made based on analysis of medical history. Prior to SAT testing, total IgE was established for each dog using a commercially available total IgE ELISA test kits (Allercept® E-screen 2G, Heska Corp., Fort Collins, USA and Asan Easy Test Canine IgE®, Asan Pharm. Corp., Hwaseong-si, Korea; Table 1). At least 1.2 mL of serum sample was collected from each dog. Four panels of 120 allergens were used for detecting serum allergen-specific IgE (Alleisa Screen™, MEDIWISS analytic, Moers, Germany). Each panel consisted of 30 selected allergens commonly existed in Korea. 60 types of food allergens were included in the panels 1 and 2 (Table 3 and 4), while 60 types of inhalant allergens were in the panels 3 and 4 (Table 5 and 6). IgE concentration was quantified colorimetrically using a BLOTrix Reader scanning system (Bioscitech GmbH, Frankfurt, Germany).

Based on the concentrations of IgE measured, results were stratified into 6 classes: a mild positive reaction was designated as class 1 or 2, a moderate reaction as class 2 or 3, and a strong positive reaction as class 3 or above. Any samples in which the positive control did not produce at least a class 4 reaction were excluded from analysis.

Intradermal skin test (IDT)

Four dogs (Dogs 1~4 from the SAT testing group) were further evaluated by IDT for comparison with SAT results. Any medication with the potential to influence IDT results was withdrawn for 21 days prior to testing.

A total of 53 water-soluble allergen extracts was used for IDT (Lenoir, North Carolina, USA). Each was administered at a dose known not to cause hypersensitivity in normal dogs (100~1000 Protein nitrogen units/mL or 1:1000 weight/volume). Histamine phosphate (27.5 µg/mL) was used as a positive control; 0.9% saline containing 0.1% phenol was used as a negative control. A scale of - to +3, relative to the mean of positive and negative controls, was used to classify wheal size. The equal or smaller size than negative control was classified as -; if it was smaller than the mean value of the positive and negative controls but it was bigger than negative control, it was classified as 1+; a wheal larger than the mean value but smaller than the positive control was classified as +2;

Table 2. Diagnostic criteria for canine atopic dermatitis [2]

Set 1	Set 2
1. Age on set <3 years	1. Age on set <3 years
2. Mostly indoor	2. Mostly indoor
3. Corticosteroid-responsive pruritus	3. pruritus with no visible lesions at onset
4. Chronic or recurrent yeast infections	4. Affected front feet
5. Affected front feet	5. Affected ear pinnae
6. Affected ear pinnae	6. Non-affected ear margin
7. Non-affected ear margin	7. Non-affected dorso-lumbar area
8. Non-affected dorso-lumbar area	

Table 1. Signalments and results of diagnostic examinations in 8 dogs

No. of Dogs	Signalments			Results of diagnostic examinations		
	Breed	Age	Sex	Total IgE kit test	Set 1 [2]	Set 2 [2]
Dog 1	French Bulldog	1-year-old	Intact female	Positive*	6/8	6/7
Dog 2	Cavalier King Charles Spaniel	2-year-old	Castrated male	Positive*	7/8	6/7
Dog 3	Mongrel	2-year-old	Spayed female	Positive*	6/8	4/7
Dog 4	Maltese	5-year-old	Castrated male	Positive*	6/8	6/7
Dog 5	Old English Sheepdog	11-year-old	Spayed female	Positive†	8/8	7/7
Dog 6	Shih Tzu	11-year-old	Castrated male	Positive†	6/8	5/7
Dog 7	Shih Tzu	2-year-old	Castrated male	Positive†	7/8	7/7
Dog 8	Pekingese	3-year-old	Intact female	Positive†	6/8	5/7

*Dogs 1~4 were tested by only Heska Allercept® E-screen 2G.

†Dogs 5~8 were tested by both Heska Allercept® E-screen 2G and Asan Easy Test Canine IgE®.

wheals larger than the positive control were classified as +3. Because some of the allergens tested differed between SAT and IDT, only the allergens that were included in both tests were analyzed and compared in this study.

Results

Serum allergen-specific IgE test (SAT)

Based on the results obtained from panels 1 and 2 (common food allergens in Korea), banana was the most fre-

quent positive allergen, stimulating a positive response in seven out of the eight dogs (87.5%; Fig. 1). On panels 3 and 4 (common inhalant allergens in Korea; Fig. 2), seven dogs (87.5%; Fig. 2) reacted positively to *Botrytis cinerea* (a fungal allergen) and six (75%; Fig. 2) reacted to *Blomia tropicalis* and *Glycyphagus domesticus* (mite allergens). Other allergens, such as *Euroglyphus maynei*, mite mixture 1 Korea, *Alternaria alternate*, mold fungi mixture 11, mold fungi mixture, and tree pollen mix 3 Korea produced a positive reaction in five of the eight

Table 3. List of allergens on panel 1 in this study

Code	English
F4	Wheat flour
F49	Apple
F92	Banana
F244	Cucumber
F27	Beef
F31	Carrot
F78	Caseine
F83	Chicken
F3_F23	Cod fish/ Crab mix
F23_F24	Crab/ Shrimp
F475	Duck
F1	Egg white
F75	Egg yolk
FX3RB	Fish mix (cod, shrimp, salmon, blue mussel and tuna)
F79	Gluten
F300	Goat milk
F504	Goose
NX_KO	Nut mixture (cashew nuts, coconut and peanuts)
F84	Kiwi
F334	Lactoferrin
F88	Lamb meat
F2	Milk
F457	Mushrooms mixed
F33	Orange
F26	Pork
F502	Pork Liver
F35	Potato
F225	Pumpkin
F213	Rabbit
F92	Rice flour

Table 4. List of allergens on panel 2 in this study

Code	English
F41	Salmon
F420	Sea Bass
F24	Shrimps
F14	Soy bean
F258	Calamari
F44	Strawberry
F54	Sweet Potato
F258	Tomato
F204	Trout
F40	Tuna
F284	Turkey
F329	Water melon
F215	Lettuce
F478	Tofu
F291	Cauliflower
F260	Broccoli
F216	Cabbage
FX400	Cheese mix
F218	Pepper
F288	Blueberry
F315	Green Beans
FX2	Meal mix
F247	Honey
F236	Whey
F94	Pear
F95	Peach
F12	Pea/ Bean
F465	Quail
F114	Sunflower seed
F2MP	Milk powder

dogs (62.5%; Fig. 2).

IDT Results and Comparison with SAT

In dog 1, positive reaction to house dust mites was indi-

Table 5. List of allergens on panel 3 in this study

Code	English
E1	Cat epithel
E2	<i>Canis domesticus</i>
E5	Dog epithel
E84_E74_73	Golden hamster/Mouse/Rat
Gx9	Mixed grasses 9 (barley, reed, smooth brome and oat)
Gx10	Mixed grasses 10 (orchard grass, timothy grass, meadow fescue grass, rye grass and kentucky grass)
Getmix	Cereals pollen mix (rye, oats, wheat, barley and maize)
Gx11	Mixed grasses 11 (sweet-scanted vernal grass, reed, rye grass and wooly holcus)
M6	<i>Alternaria alternate</i>
M47	<i>Aspergillus flavus</i>
MX11	Mould fungi mixture 11 (<i>Asp. fumigatus</i> , <i>Asp. niger</i> , <i>Asp. amstelodami</i> and <i>Asp. nidulans</i>)
M7	<i>Botrytis cinerea</i>
M5	<i>Candida albicans</i>
M208	<i>Chaetomium globosum</i>
M2	<i>Cladosporium herbarum</i>
M17	<i>Curvularia spicifera</i>
M14	<i>Epicoccum purpurascens</i>
M9	<i>Fusarium moniliforme</i>
M212	<i>Micropolyspora faeni</i>
MX1TH	Mould fungi mixture (<i>Alt. alternate</i> , <i>Clad. herbarum</i> , <i>Clad. cladosporioides</i> and <i>Stemphylium botryosum</i>)
MX7	Mould fungi mixture 7 (<i>Asp. fumigatus</i> , <i>Asp. niger</i> , <i>Asp. flavus</i> and <i>Asp. versicolor</i>)
M4mu	<i>Mucor mucedo</i>
M23	<i>Neurospora sitophila</i>
MX12	Mould fungi mixture 12 (<i>Penic. viridicatum</i> , <i>Penic. expansum</i> , <i>Penic. notatum</i> and <i>Penic. chrysogenum</i>)
M90	<i>Pityrosporum ovale</i>
M12	<i>Aureobasidium pullulans</i>
M11	<i>Rhizopus nigricans</i>
M210	<i>Sporobolomyces roseus</i>
M80	<i>S. Aureus</i> -Enterotoxin A
M81	<i>S. Aureus</i> -Enterotoxin B

cated in both tests. However, dog 1 reacted to tree pollen mix 3 Korea in SAT only and to house dust in IDT only.

In dog 2, positive reactions to *Aspergillus flavus* and cypress tree pollen were seen in both tests. Dog 2 showed 1 type of positive allergen in SAT alone and 8 types of allergens in IDT.

In dog 3, positive reactions to the house dust mite and the house dust mix were observed in both tests. Four dif-

Table 6. List of allergens on panel 4 in this study

Code	English
M266	<i>S. Aureus</i> - TSS-Toxin 1
M10	<i>Stemphylium botryosum</i>
M213	<i>Thermoactinomyces vulgaris</i>
M12	<i>Aureobasidium pullulans</i>
P4	<i>Anisakis simplex</i>
O20_O21	Grassland Cut/Hayfield Cut
O1	Cotton wool
P1	<i>Ascaris spec.</i>
D201	<i>Blomia tropicalis</i>
D73	<i>Glycyphagus domesticus</i>
D70	<i>Acarus siro</i>
DX1_KO	Mite mixture 1 Korea (D.p., D.f., D.m.)
DM1	Environmental mix1
D74	<i>Euroglyphus maynei</i>
HX	House dust
D71	<i>Lepidoglyphus destructor</i>
D72	<i>Tyrophagus putrescentiae</i>
K74	Silk
K82	Latex
TX1_KO	Tree pollen mix 1 Korea (alder, birch, oak and poplar)
TX2_KO	Tree pollen mix 2 Korea (acacia, eucalyptus, mesquite and mulberry tree)
W1_W2_W3	Ambrosia/Ragweed/Franseria
TX3_KO	Tree pollen mix 3 Korea (cedar, cypress and juniper/savin tree)
WX1_KO	Weed pollenmix 1 Korea (hibiscus, rape and soeeri)
I52_I50	<i>Aedes ssp./Culex ssp.</i>
I90	House fly (Musca)
I3	Common wasp- venom
I6X	Cockroach-mix
I9_I39_I53	Flour beetle/Wheat weevil/Black fly
O207	Water flea

ferent allergens caused a positive reaction in SAT alone: *Aspergillus flavus*, ambrosia-ragweed-franseria, cockroach mix, weed pollen mix 1 Korea, and mold fungi mix 11.

In dog 4, positive reaction to the house dust mite allergens and house dust mix was seen in both tests. Dog 4 reacted to mold fungi mix 11 and tree pollen mix 3 Korea in SAT alone.

Total agreement rates between SAT and IDT are described in Table 7.

Discussion

The atopic disease is defined as genetically predisposed tendency to develop IgE-mediated allergy to environmental allergen [1]. The environmental allergens vary significantly across countries and regions, thus it is essential to establish the geographic causative allergens in CAD. Here we present the first use of allergens prevalent in Korea for allergy testing in eight cases of CAD. This research may represent a valuable resource for Korean veterinary medicine.

Table 7. The agreements between SAT and IDT in 4 dogs

Allergen	SAT (+) IDT (+)	SAT (-) IDT (-)	SAT (+) IDT (-)	SAT (-) IDT (+)
Cat epithelia	0/4	4/4	0/4	0/4
Mixed grasses 9 (Canarygrass, Reed)	0/4	4/4	0/4	0/4
Mixed grasses 10 (Bluegrass, Kentucky/June, Orchard grass, Ryegrass, Perennial Timothy)	0/4	4/4	0/4	0/4
Cereals pollen (Oats, Common/Cultivated)	0/4	4/4	0/4	0/4
Mixed grasses 11 (Canarygrass, Reed, Ryegrass, Perennial, Sweet vernal grass)	0/4	4/4	0/4	0/4
Mould fungi mixture 11 (<i>Aspergillus</i> spp.)	2/4	0/4	0/4	2/4
<i>Fusarium moniliforme</i>	0/4	2/4	1/4	1/4
<i>Mucor</i> spp.	0/4	3/4	1/4	0/4
Mould fungi mixture 12 (<i>Penicillium</i>)	0/4	4/4	0/4	0/4
<i>Rhizopus</i> spp.	0/4	3/4	1/4	0/4
Mite Mixture 1 Korea (<i>Dermatophagoides farinae</i> , <i>Dermatophagoides pteronyssinus</i>)	3/4	0/4	1/4	0/4
House dust	2/4	0/4	1/4	1/4
Silk	0/4	4/4	0/4	0/4
Tree pollen mix 1 Korea (Poplar, Lombardy Poplar, White Birch mix, Eastern oak mix)	0/4	3/4	1/4	0/4
Tree pollen mix 2 Korea (Acacia Mulberry, Paper Mulberry, White)	0/4	3/4	1/4	0/4
Ambrosia/Ragweed/Franseria	0/4	2/4	1/4	1/4
Tree pollen mix 3 Korea (Cedar, Red Cypress, Bald)	1/4	1/4	0/4	2/4
Weed pollen mix 1 Korea (Sheep/Red sorrel)	0/4	2/4	1/4	1/4
Insects (<i>Aedes</i> spp./ <i>Culex</i> spp., House fly, Common wasp- venom, Cockroach-mix, Flour beetle/Wheat weevil/Black fly)	0/4	3/4	0/4	1/4

Table 8. Comparison of the allergens between the previous studies and this study.

Allergens	2002 [18]	2011 [19]	2014 [20]	This study
House dust mite				
<i>D. Farinae</i>	63%	49.1%	61.4%	62.5%
<i>D. pteronyssinus</i>	31%			
House dust	6%	54.5%	55.2%	37.5%
Molds	No data	67.3%	Reported only individual mold species	62.5%

There is currently no definitive diagnostic test for CAD and thus diagnosis of CAD is based on clinical manifestations, medical history and the exclusion of other potential causes of similar clinical symptoms [7]. In this study, we evaluated atopic dermatitis in eight dogs by applying Favrot's criteria [2], considered the most sensitive and

specific clinical criteria in veterinary medicine [7]. According to Favrot's criteria, when the patient meets more than 5 of 8 criteria in set 1, the sensitivity is 0.854 and the specificity is 0.791 for CAD. In set 2, the sensitivity is 0.772 and the specificity is 0.83 for CAD if more than 5 of 7 criteria are presented [2].

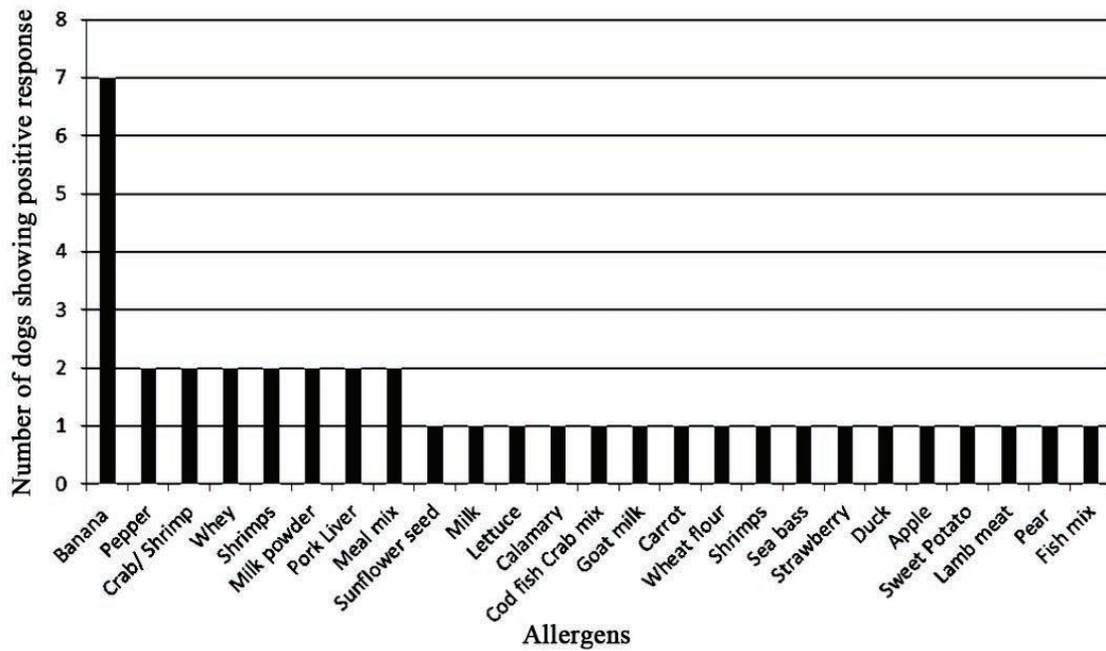


Fig. 1. The results of food allergen-specific IgE tests in this study.

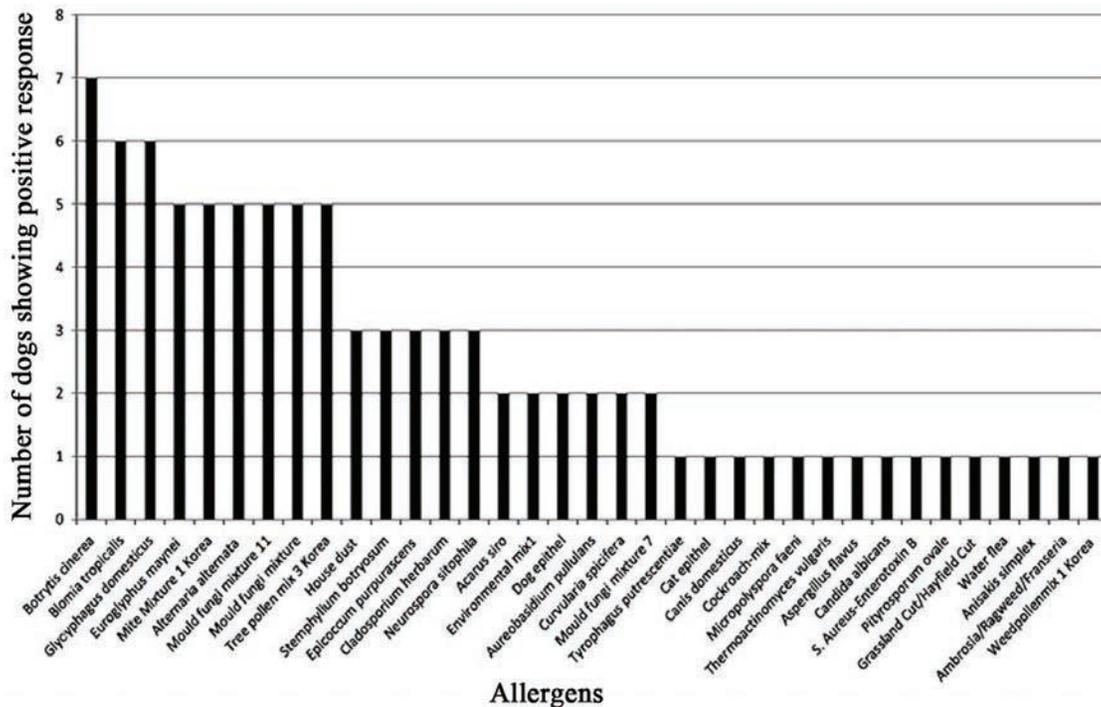


Fig. 2. The results of inhalant allergen-specific IgE tests in this study.

Allergen-specific IgE tests, such as SAT or IDT, could represent the next step towards a diagnostic method for CAD. Allergen-specific IgE tests should not be used for sole diagnostic methods of CAD, but for identification of allergens to avoid causative substances and to inform the design of immunotherapy regimens [7]. Several investigators have demonstrated the diagnostic value of both allergen-specific IgE tests for CAD, when detected allergens are used for immunotherapy or avoidance strategies [8, 9].

Currently, IDT is considered the gold-standard method for identifying causative allergens, since there is little evidence of a correlation between circulating serum IgE levels and cutaneous IgE reactivity in SAT [7]. Many studies have evaluated the agreement between SAT and IDT results and most have reported similar hypersensitivity reactions to at least some allergens in CAD [10, 11, 12, 13]. SAT may therefore have similar diagnostic value to IDT, being significantly more convenient, and is often preferred by veterinary practitioners.

In SAT of the present study, four types of mite (*Bloomia tropicalis*, *Glycophagus domesticus*, *Euroglyphus maynei*, and mite mixture 1 Korea; house dust mites), four types of mold (*Botrytis cinerea*, *Alternaria alternata*, mold fungi mixture 11, mold fungi mixture) and one type of pollen (tree pollen mix 3 Korea) promoted a reaction in more than half of dogs tested. In IDT, all four dogs reacted positively to *Dermatophagoides farina* and three reacted positively to *Dermatophagoides pteronyssinus* and house dust. The mean agreement rate between SAT and IDT in this study was 76.3% (Table 7).

According to the results of current study, banana was the most frequent positive food allergen, stimulating a positive response in seven out of the eight dogs (87.5%). Other food allergens were not detected in over half of the patients. The link between food allergens and CAD remains controversial. Classifications of food allergy and CAD have until now been completely segregated, but recently the theory that food allergens may play an important pro-inflammatory role in CAD is gaining traction [7]. In human medicine, 33% of infants and 38.7% of young children with atopic dermatitis also have a food allergy [14, 15]. Previous veterinary studies have similarly found that 30% of dogs with CAD have concurrent adverse food reactions and 13~30% of CAD patients also exhibit cutaneous adverse food reactions [16, 17]. According to one previous report [18], however, SAT showed very low sensitivity (6.7%) and high specificity (91.4%) in canine adverse food reaction study. The positive and negative predictive values were 15.4% and 80.7%, respectively [18]. These results indicated that a positive result of canine SAT in food allergy could not be very helpful. The negative result of SAT of food allergens demonstrates that those antigens are tolerated well [18],

thus we could utilize the negative result data in practice. In the present study, we evaluated SAT of food allergens in dogs and results were described in Fig. 1. Because of low sensitivity, we suggested that SAT results of food allergens in this study should apply only as reference data.

One previous study [19] demonstrated allergens associated with CAD in 35 dogs using IDT with 42 types of Korean allergen extracts. In 2011, Kim *et al* [20] also tested 39 common Korean allergens in 58 dogs with CAD using IDT. Recently, investigations of SAT for 101 CAD dogs were performed in Korea with 92 inhalant and food allergens [21]. However, there has not been the trial to choose allergens based on domestic environment and also not report comparing the results between IDT and SAT for the same dogs in Korea. Comparing these previous reports with the current study, we demonstrate that the positive ratio of specific allergens showed similar results (Table 8).

Total IgE ELISA test kits were used to support a diagnosis of CAD in this study; serological total IgE testing is usually used as a screening method in human allergic disease. Several studies have reported that total serum IgE levels may be predictive of positive reactions in SAT, clinical severity, and diagnosis of allergic diseases, although their value as diagnostic tools in humans is limited by variation in responses across different races [22, 23]. In veterinary medicine, conversely, total IgE serological tests have been widely reported as unreliable, detecting no significant difference in total serum IgE levels between normal and atopic dogs [10]. Further studies are needed to evaluate the diagnostic value of total IgE levels relative to positive results of SAT in CAD.

This study represents the first evaluation of Korean CAD allergens by SAT which composed of selected Korean type 120 allergens and the first comparison of SAT with IDT in Korean veterinary medicine. The limitations of this study include a small sample size and the omission of a standard for comparison between SAT and IDT. Further study using larger cohorts and immunotherapy trials based on causative allergens detected by SAT will be necessary in the future.

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