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RESEARCH ARTICLE

Specific Dog Allergen Immunoglobulin G Antibodies in Patients with Allergic Conjunctivitis

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Abstract:

Purpose:

The purpose of the study was to examine the role of total tear IgE, and specific serum dog IgG and IgE antibodies on the severity of allergic conjunctivitis.

Methods:

This study enrolled healthy subjects (control group, N=13), the patients with seasonal allergic conjunctivitis (seasonal group, N=13), and patients with perennial allergic conjunctivitis (perennial group, N=13). Skin prick test, tear IgE level, and serum specific dog IgE and IgG levels were examined. The severity of allergic conjunctivitis using a grading score (0-30) was also examined.

Results:

The levels of serum dog-specific IgE and IgG, and total tear IgE of the seasonal and perennial groups were higher as compared to those of the control group (all $p<0.05$). The levels of serum dog-specific IgG of the perennial group were higher than those of the seasonal group (0.4 ± 0.6 vs. 0.0 ± 0.0). Multivariate analysis confirmed that the skin prick test result for dog allergen was related to the serum dog-specific IgG levels, but not IgE levels ($p<0.01$). The severity of allergic conjunctivitis was related to the serum level of dog-specific IgG antibodies ($p<0.01$).

Conclusion:

It was concluded that dog-specific IgG antibodies level may be associated with the severity of dog-related perennial allergic conjunctivitis.

Keywords: Allergic conjunctivitis, Specific IgE, Specific IgG, Dog, Seasonal allergy, Perennial allergy.

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1. INTRODUCTION

Immunoglobulins are complex proteins that recognize cell surface antigens and protect the host against various pathogens as well as against malignancy. Human immunoglobulin (Ig) has five classes IgA, IgG, IgM, IgD, and IgE [1 - 3]. IgG is involved in protection against infection by bacteria, fungi, and viruses through immobilization and opsonization of pathogens to which IgG antibodies bind. Specific IgG antibodies to viruses or other pathogens can be detected during the acute phase of infection. It has been also reported IgG increased in patients with wheezing in childhood [4] or with food allergy [5 - 7]. Recently, a screening test using IgG measurement has been used to diagnose allergic diseases [8, 9], but measuring the serum IgG level for the assessment of allergic diseases has not yet gained popularity.

Allergic conjunctivitis is classified as seasonal, perennial, or atopic conjunctivitis. IgE level increases in seasonal allergic conjunctivitis [2, 3]. It has been previously suggested that specific IgG antibodies may be involved in perennial allergic conjunctivitis by measuring the serum level of cat-specific IgE antibodies [10].

According to the Japan Pet Food Association, there were approximately 10.9 million dogs and 9.7 million cats as pets in Japan in 2013, with at least one dog in 15.8% and at least one

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cat in 10.1% of Japanese households [11]. Thus, more people own dogs than cats in Japan, and dog allergens are a major cause of indoor allergen-induced allergic diseases along with cat allergens [12]. However, it has not been examined whether dog allergens are associated with allergic conjunctivitis. In this study, the clinical impact of dog-specific IgG antibodies against allergic conjunctivitis has been investigated.

2. MATERIALS AND METHODS

2.1. Study Design

This was a prospective, nonrandomized, cross-sectional, consecutive case series study conducted at Tokyo Women's Medical University Medical Center East Hospital and affiliated hospitals. This study was performed in accordance with the Helsinki Declaration. Our institutional review board approved the study protocol and informed consent was obtained from each subject.

2.2. Subjects

Patients were divided into the following three groups: patients with seasonal allergic conjunctivitis (seasonal group), patients with perennial allergic conjunctivitis (perennial group), and age- and sex-matched healthy non-smoking volunteers (control group) as shown in Table **1**.

2.3. Diagnosis of Allergic Conjunctivitis

Allergic conjunctivitis was diagnosed according to the Japanese guideline for allergic conjunctival diseases [13, 14]. Additionally, we classified the 5 categories (papillae, and giant papillae, follicles, edema, and hyperemia in palpebral conjunctiva), two categories (chemosis and hyperemia in the bulbar conjunctiva), and three categories (corneal erosion, limbal edema Trantas' dots in the limbus) into 4 grades (0, 1, 2, 3) according to a published criteria for clinical assessment of ocular allergy [14 - 16]. The total score was calculated, consisting of the scores of 10 categories in the right eye (0-30) [15].

2.4. Measurements

The total IgE level in tear fluid (total tear IgE) was measured with the Allerwatch® test according to the manufacturer's instructions [17 - 26]. The level of dog-specific IgE antibodies was measured with the ImmunoCAP Rapid® immunochromatography assay kit (Phadia Diagnostics, Uppsala, Sweden) [27, 28] and the level of dog-specific IgG antibodies was measured with an enzyme-linked immunosorbent assay (ELISA) from US BioTek Laboratories (Seattle, WA) according to the manufacturer's instructions [28, 29]. A skin prick test for dog allergens was performed using dog dander extract (1:20 wt/vol; Torii Pharmaceutical Co., Ltd., Tokyo, Japan).

2.5. Statistical Analysis

The two-tailed unpaired Student's *t*-test, one-way analysis of variance, and Scheffe's multiple comparison test were performed for the comparison among groups. The chi-square test of independence or Fisher's exact probability test was used for the analysis of frequencies. Semiquantitative analysis was performed by the two-tailed Mann-Whitney U test for two groups and Kruskal-Wallis one-way analysis of variance by ranks for three groups. Diagnostic accuracy was evaluated by means of positive and negative predictive values, specificity, and sensitivity. Correlations were evaluated by Pearson's correlation coefficients. The differences between the two correlations were analyzed with Fisher's Z transformation. The probable associated factors for the total score and the skin prick test result were analyzed using the multivariate logistic regression analysis. P values of less than 0.05 were regarded as significant. SAS System software was used for all analyses (SAS Institute Inc., Cary, North Carolina, USA).

3. RESULTS

3.1. Comparison Of Each Test Among The Control, Seasonal, And Perennial Groups

There were significant differences in the total tear IgE positive rate among the control, seasonal, and perennial groups (0.0%, 100.0%, and 100.0%, $p<0.0001$) (Table **1**). A positive result for serum dog-specific IgE antibodies was significantly higher in the seasonal and perennial groups (30.8 and 38.5%) than in the control group (0.0%, $p=0.0482$) (Table **1**). Positivity for serum dog-specific IgG antibodies was significantly higher in the perennial group (30.8%) than in the control or seasonal group (0.0% and 0.0%, $p=0.0116$). The sensitivity and specificity of serum dog-specific IgG against skin prick test results were both higher than those of serum dog-specific IgE (50.0% *vs*. 25.0% and 100.0% *vs*. 77.4%, Table **2**). The positive and negative predictive values of serum dog-specific IgG were also higher than those of serum dog-specific IgE (100.0% *vs*. 22.2% and 88.6% *vs*. 80.0%, Table **2**). The comparisons of the total tear IgE levels Fig. (**1A**) and the serum levels of dog-specific IgE Fig. (**1B**) and IgG antibodies Fig. (**1C**) among the three groups are shown in Fig. **1A-1C**). A Receiver Operating Characteristic (ROC) curve was made from the data used in (Table **2**). Fig. (**2**) shows an ROC curve for True-Positive Rate (TPR) and False-Positive Rate (FPR) of allergic tests in predicting true skin prick test results.

Table 1. Clinical profile of each group.

	Control Group	Seasonal Group	Perennial Group	P-value
Number of Subjects	13	13	13	-
Gender Male/Female	5/7	5/7	5/7	*1.0000
Age (years)	29.4 ± 8.6	27.3 ± 10.8	27.1 ± 9.0	**0.8075

(Table 1) contd.....

	Control Group	Seasonal Group	Perennial Group	P-value
Dog at home	3	3	4	-
Allergy Test	-	-	-	-
Total tear IgE	0 (0.0%)	13 (100%)	13 (100.0%)	*<0.0001
Serum dog-specific IgE	0 (0.0%)	4 (30.8%)	5 (38.5%)	*0.0482
Serum dog-specific IgG	0 (0.0%)	0 (0%)	4 (30.8%)	*0.0116
Skin prick test (Dog)	1 (7.7%)	2 (15.4%)	5 (38.5%)	*0.0058

Number of patients (percentage) or mean ± standard deviation (SD). *Chi-square test of independence or Fisher's exact probability test. **One-way analysis of variance and Scheffe's multiple comparison test. NS=Not significant.

Table 2. Results of the immunoglobulin assays.

	Total tear IgE	Serum dog-specific IgE	Serum dog-specific IgG
Sensitivity	87.5%	25.0%	50.0%
Specificity	38.7%	77.4%	100.0%
False-positive rate	61.3%	22.6%	0.0%
False-negative rate	12.5%	75.0%	50.0%
Positive predictive value	26.9%	22.2%	100.0%
Negative predictive value	92.3%	80.0%	88.6%
Positive likelihood ratio	1.4	1.1	- (∞)

Detection of IgE or IgG antibody and positive/negative results of the skin prick test for dog allergen in all subjects (N=39).

3.2. Comparison Of Each Test Between The Seasonal And Perennial Groups

Each parameter was compared between the seasonal and perennial groups. The grade of serum dog-specific IgG antibodies was higher in the perennial group (0.4 ± 0.6) than in the seasonal group (0.0 ± 0.0), but the difference was not significant (p=0.1824, Fig. **1C**). The average grades of total tear IgE (1.8 ± 0.4 *vs*. 1.4 ± 0.5, P=0.3173, Fig. **1A**) and serum dog-specific IgE antibodies (0.4 ± 0.7 *vs*. 0.5 ± 0.7, P=0.6816, Fig. **1B**) showed no significant difference between the two groups.

The mean wheal diameters for dog allergens in the skin prick test were larger in the perennial group than in the seasonal group (5.6 ± 3.8 mm *vs* 3.6 ± 1.9 mm, p=0.0266) as shown in Fig. (**3**).

3.3. Relationships Between Total Symptoms Scores And Class Of Dog-Specific Ige Or Igg

The allergy patients were divided into three groups based on the class of specific IgE for dog allergens (class 0 in 17 patients, class 1 in 6 patients, and class 2 in 3 patients). They were also divided into three groups based on the class of specific IgG for dog allergens (class 0 in 22 patients, class 1 in 3 patients, and class 2 in 1 patient, with no patients in classes 3-6 (Fig. **4**). The total score was highest in patients with class 3 IgG, and a significant difference was noted in the total score among the three IgG class groups (p=0.0100). However, there was no significant difference among the three IgE class groups p=0.8084, (Fig. **4**).

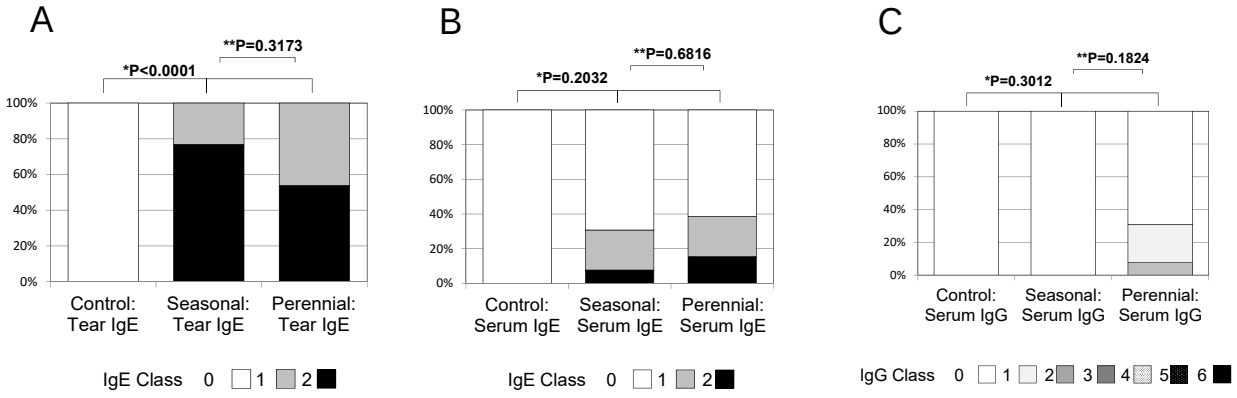

Fig. (1). Comparison of the grade of positivity for total tear immunoglobulin E (IgE) (**A**), and serum dog-specific IgE (**B**) and IgG scores (**C**) among the control, seasonal, and perennial groups. The results were compared among the three groups by Kruskal-Wallis one-way analysis of variance*, while the seasonal and perennial groups were compared by the two-tailed Mann-Whitney U test**.

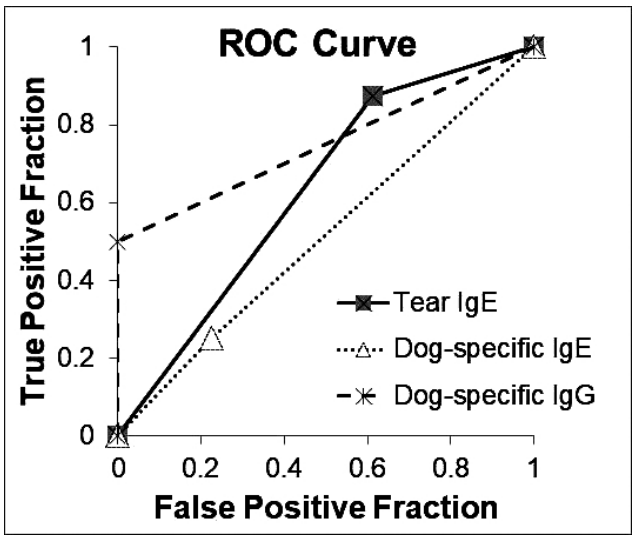

Fig. (2). ROC curve for True-Positive Rate (TPR) and false-positive rate (FPR) of allergic tests in predicting true skin prick test result.

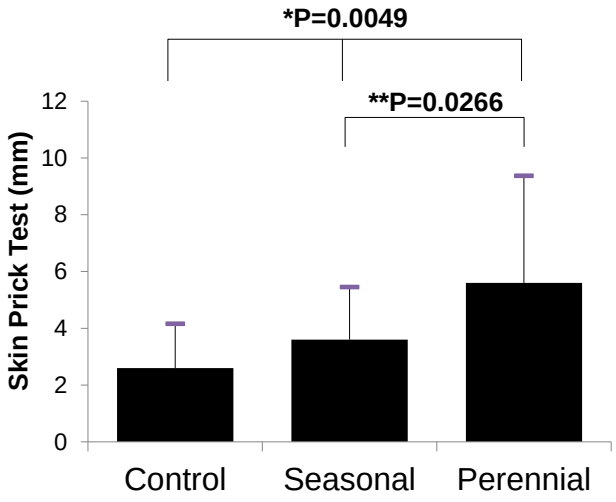

Fig. (3). Comparison of the mean wheal diameter in the skin prick test for dog allergen among the control, seasonal, and perennial groups. The results were compared among the three groups by Kruskal-Wallis one-way analysis of variance*, while the seasonal and perennial groups were compared by the two-tailed Mann-Whitney U test**.

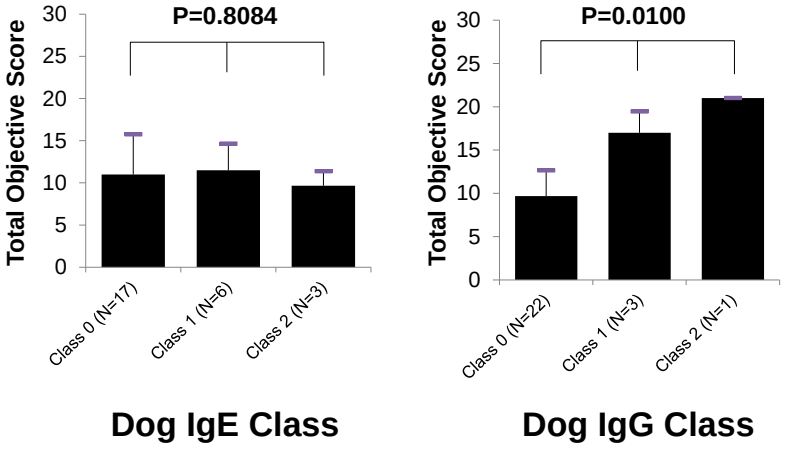

Fig. (4). Comparison of the mean total scores for allergic conjunctivitis among groups with different classes of serum dog-specific IgE or IgG. Patients were divided into three groups according to the dog-specific IgE or IgG class as described in Methods. The results are expressed as the mean ± SD. A comparison among the groups was done by the Kruskal-Wallis one-way analysis of variance.

3.4. Comparison Of Each Parameter Between Patients With Or Without A Dog At Home

Table **3** shows the comparison of various parameters between patients who kept a dog at home (n=7) and those without a dog (n=19). There were no significant differences in the positivity and scores of all tests between patients who kept a dog at home and those without a dog.

3.5. Clinical Scores In Igg-Positive And Igg–Negative Patients

Table **4** shows the comparison of the clinical features of allergic conjunctivitis between patients who had a positive (n=4, IgG-positive group) or negative result for serum dog-specific IgG antibodies (n=22, IgG-negative group). The scores of clinical features of allergic conjunctivitis were significantly higher in the IgG-positive group than in the IgG-negative group.

3.6. Relationships Between Skin Prick Test Results and Immunoglobulin Levels

In all patients, the mean wheal diameter for dog allergens in the skin prick test was strongly correlated with the total tear IgE level (r=0.38, p=0.0185), and the serum dog-specific IgG antibody titer (r=0.81, p<0.0001), but was not correlated with the serum dog-specific IgE antibody titer (r=0.21, p=0.1989) (Table **5**). The mean wheal diameter in the skin test showed a stronger correlation with serum dog-specific IgG (r=0.81, p<0.0001, n=39) than with serum dog-specific IgE (r=0.21, p=0.1989, n=39) (wheal diameter and IgG *vs.* wheal diameter and IgE; p=0.0001, Fisher's z statistics). Furthermore, the

Table 3. Comparison of results between patients with or without a dog at home.

-	Dog owner	No dog at home	P-value
Number of Patients	7/26 (26.9%)	19/26 (73.1%)	-
Total tear IgE	-	-	-
Positive rate	7/7 (100%)	19/19 (100%)	-
Score (mean ± SD)	2.1 ± 1.7	1.6 ± 0.5	**0.7100
Serum dog-specific IgE	-	-	-
Positive rate	2/7 (28.6%)	7/19 (36.8%)	*0.5375
Score (mean ± SD)	0.6 ± 0.9	0.4 ± 0.6	**0.7131
Serum dog-specific IgG	-	-	-
Positive rate	2/7 (28.6%)	2/19 (10.5%)	*0.2870
Score (mean ± SD)	0.3 ± 0.5	0.2 ± 0.5	**0.8654
Skin prick test	-	-	-
Positive rate	4/7 (57.1%)	3/19 (15.8%)	*0.0572
mm (mean ± SD)	6.7 ± 3.7	3.7 ± 2.6	**0.0966

Number of patients (percentage) or mean ± standard deviation (SD). *Fisher's exact probability test. **Two-tailed Mann-Whitney U test.

Table 4. Scores for allergic conjunctivitis in IgG-positive and IgG–negative patients.

-	IgG-positive	IgG-negative	P-value
Number of Patients	4	22	-
Palpebral conjunctiva	-	-	-
Hyperemia	2.5 ± 0.5	1.9 ± 0.6	0.1098
Edema	2.5 ± 0.5	1.5 ± 0.6	0.0360
Follicles	2.5 ± 0.5	1.3 ± 0.4	0.0183
Papillae	3.0 ± 0.0	1.0 ± 0.6	<0.0001
Giant papillae	1.8 ± 0.4	0.0 ± 0.2	0.0055
Bulbar conjunctiva	-	-	-
Hyperemia	2.5 ± 0.5	1.9 ± 0.5	0.1097
Chemosis	2.0 ± 0.7	1.4 ± 0.8	0.2229
Limbus	-	-	-
Trantas' dots	0.3 ± 0.4	0.4 ± 0.6	0.7020
Edema	1.0 ± 0.7	0.3 ± 0.5	0.1719
Cornea	-	-	-
Epithelial damage	0.0 ± 0.0	0.0 ± 0.2	0.1694
Total Score	18.0 ± 2.7	9.7 ± 3.0	0.0079

The two-tailed unpaired *t*-test was used to compare the clinical features of allergic conjunctivitis between patients who were positive and negative for serum dog-specific IgG. Ocular findings were assessed by slit lamp examination on a scale of 0-3 (0=normal, 3=severe) and the total score was calculated as the sum of the individual scores (0-30 points).

mean wheal diameter for dog allergens was associated with the serum level of dog-specific IgG (n=39, Odds Ratio [OR]=298.5, p<0.0001), however, no correlation was noted with IgE level by the multivariate analysis (Table **5**).

3.7. Relationships Between Total Symptom Score And Immunoglobulin Levels.

Table **6** shows the correlations between the total score and immunoglobulin levels, as well as the results of multivariate analysis. Fig. (**5**) shows a simulation using multivariate logistic regression models for the relation of the total score to the IgG and IgE scores in patients with seasonal or perennial allergic conjunctivitis (n=26). This analysis showed that an increase of the serum dog-specific IgG score by 1 point resulted in an increase of the total score by 5.32 points (OR=205.2, p=0.0005, Table **6** and Fig. (**5**). In contrast, an increase of the dog-specific IgE score by 1 point only increased the total score by 0.05 points, and the total score was not correlated with the IgE score (OR=0.8, p=0.7701) (Table **4**).

Table 5. Correlations between skin prick test results and immunoglobulin levels, as well as the results of multivariate analysis.

-	Correlation Coefficient		Multivariate Analysis		
Variables	**R**	***P* value**	**OR**	**(95% CI)**	***P* value**
All Subjects (N=39)	-	-	-	-	-
Total tear IgE	0.38	0.0185	1.6	(0.8 – 3.2)	0.1801
Serum specific IgE	0.21	0.1989	1.9	(0.7 – 4.9)	0.1947
Serum specific IgG	0.81	<0.0001	298.5	(72.7 – 1224.8)	<0.0001
Seasonal and Perennial Groups (N=26)	-	-	-	-	-
Total tear IgE	0.16	0.4299	1.5	(0.3 – 6.9)	0.6168
Serum specific IgE	0.10	0.6180	1.9	(0.6 – 5.4)	0.2405
Serum specific IgG	0.85	<0.0001	298.5	(64.2 – 1387.4)	<0.0001
Seasonal Group (N=13)	-	-	-	-	-
Total tear IgE	0.28	0.3557	1.4	(0.1 – 16.1)	0.7677
Serum specific IgE	0.62	0.0248	5.3	(1.0 – 27.6)	0.0481
Serum specific IgG	-	-	-	-	-
Perennial Group (N=13)	-	-	-	-	-
Total tear IgE	0.31	0.3100	1.1	(0.1 – 15.8)	0.9457
Serum specific IgE	-0.14	0.6379	0.8	(0.1 – 4.5)	0.7870
Serum specific IgG	0.90	<0.0001	243.6	(29.2 – 2032.1)	0.0002

R=Two-tailed Pearson's correlation coefficients were calculated for the association between the mean wheal diameter for dog allergen in the skin prick test and each immunoglobulin score. OR=odds ratio; CI=confidence interval.

Table 6. Correlations between the total score and immunoglobulin levels, as well as the results of multivariate analysis.

	Correlation Coefficient		Multivariate analysis		
Variables	**R**	***P* value**	**OR**	**(95% CI)**	***P* value**
All Subjects (N=39)	-	-	-	-	-
Total tear IgE	0.84	<0.0001	207.5	(66.2 – 650.8)	<0.0001
Serum specific IgE	0.27	0.0984	1.1	(0.2 – 5.2)	0.9480
Serum specific IgG	0.54	0.0004	204.5	(19.9 – 2103.9)	<0.0001
Seasonal and Perennial Groups (N=26)	-	-	-	-	-
Total tear IgE	0.38	0.0562	14.7	(1.0 – 225.0)	0.0536
Serum specific IgE	-0.06	0.7704	0.8	(0.1 – 4.9)	0.7701
Serum specific IgG	0.65	0.0003	205.2	(13.8 – 3043.0)	0.0005
Seasonal Group (N=13)	-	-	-	-	-
Total tear IgE	0.37	0.2069	7.7	(0.1 – 648.2)	0.3280
Serum specific IgE	0.28	0.3472	2.2	(0.1 – 43.1)	0.5746
Serum specific IgG	-	-	-	-	-
Perennial Group (N=13)	-	-	-	-	-
Total tear IgE	0.58	0.0372	40.1	(0.4 – 4351.8)	0.1083
Serum specific IgE	-0.29	0.3355	0.3	(0.0 – 6.6)	0.4277
Serum specific IgG	0.69	0.0097	68.9	(1.7 – 2828.5)	0.0298

R=Two-tailed Pearson's correlation coefficients were calculated for the association between the total score for allergic conjunctivitis and the other allergic tests. OR=odds ratio; CI=confidence interval.

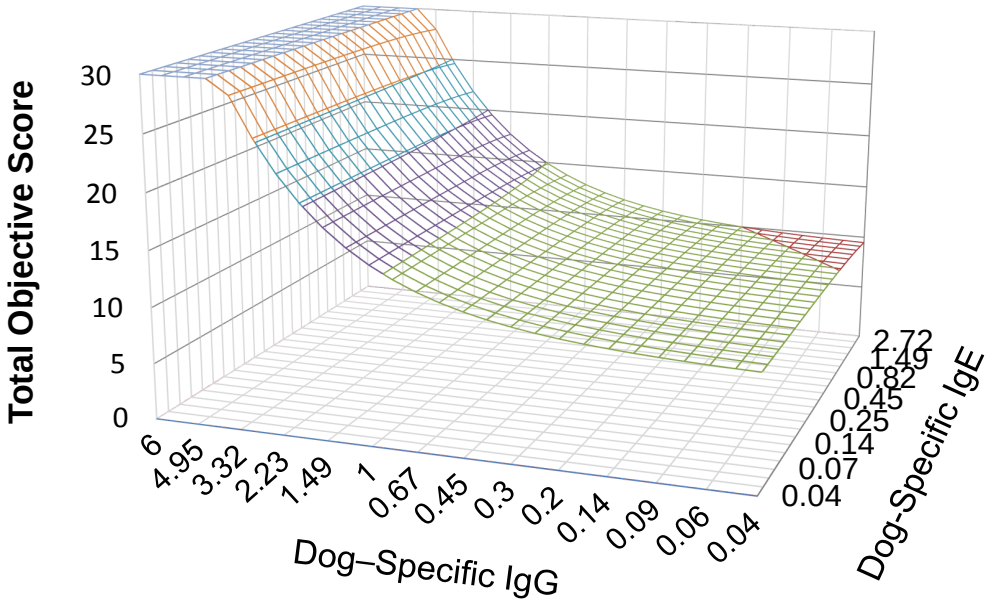

Fig. (5). Predicted probability of each total score in relation to the class of dog-specific IgE and IgG antibodies. Predicted values were calculated by multivariate logistic regression analysis.

4. DISCUSSION

This study revealed that patients with perennial allergic conjunctivitis were more likely to be positive for serum dog-specific IgG and had higher levels of dog-specific IgG antibodies than the control group and the seasonal allergic conjunctivitis group. The total severity score of allergic conjunctivitis and the skin prick test reaction to dog allergen was more strongly correlated with the dog-specific IgG levels as compared with the dog-specific IgE levels. In addition, the multivariate analysis also showed the dog-specific IgG score to be significantly correlated with the skin reaction to dog allergen showing the severity of allergic conjunctivitis in both the seasonal and perennial groups. Therefore, specific IgG antibodies are more closely related to the severity of perennial allergic conjunctivitis than specific IgE antibodies.

The positive rate of allergic conjunctivitis associated with a positive SPT for dog allergen was 26.9% (7/26) in this study. Warm and associates reported that dog allergen was positive in 13% of 483 patients investigated in 1994 and in 25% of 463 patients assessed in 2009 by skin prick test [30,31]. In Asian subjects, Park and associates demonstrated that dog allergen was detected in 20.7% in allergic rhinitis patients from Seoul, Korea by skin prick test [32]. In addition, the skin prick test for dog allergen was detected in 5.0% (50/977) chronic rhinitis patients chronic rhinitis from Hong Kong [33]. According to the findings of the Thematic Household Survey on dogs and cats conducted by the Hong Kong Census and Statistics Department from October to December 2010, 7.1% of households kept dogs [34]. Hong Kong has a pet dog population of 247,500, which is very small as compared with the estimated 10.9 million dogs in Japan. Our results were similar to the skin prick test results by these previous reports.

Total tear IgE, serum dog-specific IgE and IgG, and the skin prick test for dog allergen were compared between the seasonal and perennial groups. There were no significant differences in total tear IgE (Fig. **1**) and serum dog-specific IgE (Fig. **2**) between the two groups. However, the serum level of dog-specific IgG antibodies was higher in the perennial group than in the seasonal group (Fig. **3**). In addition, the mean diameter of the wheal reaction to dog allergen in the skin prick test was larger in the perennial group than in the seasonal group (p=0.0266), (Fig. **4**). The mean wheal diameter for dog allergen in this test was correlated with the serum level of dog-specific IgE antibodies in the seasonal group (r=0.62), and with serum dog-specific IgG antibodies in the perennial group (r=0.90), (Table **5**). The total score was not significantly correlated with any test in the seasonal group, but was strongly correlated with the serum level of dog-specific IgG antibodies in the perennial group (r=0.69), (Table **6**). These results suggest that indoor allergens such as dog allergens are more frequently associated with perennial allergic conjunctivitis than with seasonal allergic conjunctivitis. Small allergen particles such as animal dander and house dust mites can stay in the environment for a long time and easily float in the air or contaminate bedding and mattresses. Therefore, indoor allergens such as dog allergens could trigger allergic reactions at any time in people with perennial allergic conjunctivitis. These findings also support our previous observations on serum levels of dog mite-specific IgE in the autumn [3].

The clinical significance of serum dog-specific IgG antibodies and the relationship with dog-specific IgE antibodies were evaluated. It was found that the sensitivity and specificity for the diagnosis of dog antigen-induced allergic conjunctivitis were both higher for dog-specific IgG antibodies than dog-specific IgE antibodies (Table **2**). The skin prick test reaction to dog allergen was strongly correlated with the serum level of dog-specific IgG antibodies (r=0.81) than with that of dog-specific IgE antibodies (r=0.21). The clinical features of allergic conjunctivitis showed higher scores in patients who

were positive for dog IgG than in IgG-negative patients (Table **3**). Furthermore, the total score was strongly correlated with the serum level of dog-specific IgG antibodies (r=0.54) than with that of dog-specific IgE antibodies (r=0.270, (Table **6**). These results suggest that the measurement of specific IgG may be superior to the measurement of specific IgE for the diagnosis of indoor allergen-induced perennial allergic conjunctivitis and for the assessment of its severity. Specific IgE mediates type 1 hypersensitivity and is primarily responsible for immediate-type allergic diseases [33]. Type I hypersensitivity is accompanied by a shift of the T helper (Th) 1/Th2 balance toward a Th2-dominant state. In contrast, specific IgG is involved in protective immunity and also mediates type II and type III hypersensitivity reactions [34]. The production of specific IgG is regulated by Th1 cells after class switching and is responsible for the secondary immune response. Thus, our results could be explained by a shift in the balance of Th1 and Th2 cells toward a Th1-dominant state. Chronic or delayed-type hypersensitivity reactions are mediated by Th1 cells. Accordingly, a mild Th1 response to indoor allergens may induce continuous IgG production in chronic perennial allergy rather than a Th2 response associated with IgE production. The known mechanisms of the Th1/Th2 pathways involved in perennial allergy and our results suggest that specific IgG is more closely associated with the development of perennial allergy than specific IgE.

Sensitization to dog allergens was compared between patients who kept dogs at home and those without a dog, revealing that there was no significant difference in the positive rate of dog keeping between the seasonal group (23.1%) and the perennial group (30.8%), (Table **1**). There are conflicting reports about whether keeping pets increases or decreases the risk of allergy [37 - 53]. A recent meta-analysis showed that exposure to cats had a preventive effect on childhood asthma, while exposure to dogs increased the risk of asthma [39]. Lodge *et al*. searched the MEDLINE database to find studies concerning pet exposure and the risk of asthma, and concluded that keeping dogs may reduce the onset of allergic disease in persons without a family history of allergy [40]. Regarding the relationship between exposure to dogs and subsequent sensitization to allergy, Ownby *et al*. reported that exposure to 2 or more dogs or cats in the first year of life reduced the subsequent risk of allergic sensitization to multiple allergens [41]. In addition, Wegienka *et al*. performed a cohort study and reported that exposure to dogs or cats in early life was not associated with an increased risk of sensitization to animals [42].

Finally, we examined whether the serum level of dog-specific IgG antibodies was correlated with the objective score for allergic conjunctivitis. It was found that the total severity score of allergic conjunctivitis was higher in patients with dog-specific IgG positive than in those with IgG-negative (Table **4**). Additionally, the levels of dog-specific serum IgG were correlated with a total severity score of allergic conjunctivitis (Table **6**). Thus, specific IgG levels may increase with the severity of allergic conjunctivitis.

Our study has several limitations. Firstly, two methods of ELISA were used for IgG and immunochromatography for IgE because an immunochromatography assay kit for dog-specific IgG is not commercially available. Secondly, the sample size was too small and may affect the statistical power of the study. Thus, the interpretation of the findings of our trial may be limited by the small number of patients. Thirdly, our results may not be generalizable to other allergic diseases.

CONCLUSION

In conclusion, the measurement of dog-specific IgG levels may be useful in understanding the symptoms of perennial allergic conjunctivitis induced by dog allergens. In the future, the measurement of dog-specific IgG in tears may be useful for the diagnosis of dog-related perennial allergic conjunctivitis [54, 55].

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This trial was approved by the regional ethics committee (H24-2612) and is registered with the UMIN Clinical Trials Registry, number UMIN000013687.

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All human research procedures were followed in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

Informed consent was obtained from each subject.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Tatsuya Mimura and Hidetaka Noma designed the study, performed the analysis and wrote the manuscript. Atsushi Mizota contributed to the critical revision of the manuscript. All the authors read and approved the final manuscript.

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