



Short communication

Food allergen-specific serum IgG and IgE before and after elimination diets in allergic dogs

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ABSTRACT

Serum food allergen-specific antibody testing is widely offered to identify suitable ingredients for diets to diagnose adverse food reaction (AFR) in dogs with allergic skin disease. Antibody concentrations in blood samples obtained during an unsuccessful diet to help in the choice of diet changes may be influenced by the previous diet. The objective of this paper was to measure food antigen-specific IgE and IgG for the most commonly used 16 food antigens before and after an elimination diet. Levels of food-specific serum IgE and IgG antibodies were measured by enzyme-linked immunosorbent assay (ELISA). Dogs had detectable IgE antibodies to beef, pork, lamb and cows' milk; and detectable IgG antibodies to beef, pork, lamb, cows' milk, chicken and turkey. Of 19 dogs with complete data sets, 14 dogs showed clear improvement during diet and in 7 dogs AFR could be diagnosed by deterioration on rechallenge and subsequent improvement on refeeding the diet. Serum was obtained before and 6–8 weeks after beginning such a diet. There was no significant difference in pre- and post-diet levels for any of the individual allergens nor for the total IgE and IgG concentrations of all antigens ($P=0.55$ and $P=0.53$ respectively). In these 19 dogs in which an elimination diet was used for the diagnosis of food allergy and in which 14 were probably food allergic and 7 were proven food allergic there were no significant differences in food-specific antibodies before and after an elimination diet of 6–8 weeks.

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1. Introduction

Adverse food reaction (AFR) is defined as any clinically abnormal response attributed to the ingestion of a food or food additive. AFRs are categorized as either food allergy or food intolerance reactions. Food allergy/food hypersensitivity is immunologically mediated in contrast to non-immunologically mediated food intolerance reactions such as food poisoning, pharmacological, metabolic

reaction or idiosyncratic reactions (Hilliier and Griffin, 2001). Various studies reported different incidences of cutaneous AFRs in veterinary practice (Loeffler et al., 2004; Chesney, 2002; Wilhelm and Favrot, 2005).

Atopic disease (AD) is a common problem in small animal practice and atopic disease caused by food antigens versus AD caused by environmental antigens may be difficult to distinguish clinically (Picco et al., 2008). Historical information such as diet changes, non-seasonal clinical signs or gastrointestinal abnormalities such as vomiting or diarrhoea may increase the index of suspicion for a diagnosis of AFR (Hilliier and Griffin, 2001). The gold-standard of diagnosis for AFR in dogs is response to a strict elimination diet fed for up to a minimum of 6–8 weeks followed

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by a relapse following provocation challenge with the previous diet for up to 14 days (Rosser, 1993). Dietary trials with home-cooked elimination diets (Rosser, 1993; Chesney, 2002), hydrolysed protein diets (Loeffler et al., 2004; Biourge et al., 2004) and commercial diets with unusual protein and carbohydrate sources (Leistra et al., 2001) are all reported to be useful. A significant improvement during an elimination diet and a recurrence of clinical signs after challenge is strongly supportive of a diagnosis of AFR. If improvement is again observed upon feeding the elimination diet, the diagnosis is confirmed. Serological testing is offered for antibodies against a variety of food antigens. However, many food ingredients provoke IgE and IgG antibodies in patients who do not show any cutaneous or gastrointestinal signs (Foster et al., 2003). In one study, increases in soy and corn-specific serum IgE concentrations were observed in sera from individual dogs post-challenge when measured by ELISA (Jackson et al., 2003). In another study, corn-specific serum IgE decreased in five dogs with suspected food hypersensitivity to corn in response to elimination of corn protein from the diet (Jackson and Hammerberg, 2002). The positive and negative predictability of a patch test and serum test was tested in a recently presented study (Schaefer et al., 2011). The high sensitivity and negative predictability of the patch test and to a lesser degree of serum testing for food antigen-specific antibodies indicates, that if an antigen does not show a reaction on this test, it is a good choice for an elimination diet (Schaefer et al., 2011). A clinician may consider serum testing during or directly after an elimination diet due the lack of response to this diet, to identify suitable allergens for a diet change. However it is not known if serum antibodies against foodstuffs will decrease during an elimination diet rendering results of serum testing difficult to interpret.

The aim of this paper was to investigate whether an elimination diet of 6–8 weeks influences the serum levels food antigen-specific serum IgE and IgG antibodies.

2. Materials and methods

2.1. Study objects

Dogs suspected to have an AFR or AD caused by environmental allergens based on their history, clinical signs and exclusion of differential diagnoses such as cutaneous infections or ectoparasites were included in the study. Other differential diagnoses were excluded by ectoparasite control, results of cutaneous cytology, response to antibiotic therapy, results of fungal cultures, blood biochemistry, measurements of thyroid hormones and others tests as appropriate. The dogs were presented to the Dermatology Service of the Centre for Clinical Veterinary Medicine of the Ludwig Maximilian University Munich and two small animal practices in Berlin. Systemic glucocorticoids were not permitted for three weeks before and during the diet trial. Other anti-inflammatory therapy (fatty acid supplementation or antihistamines) was discontinued two weeks prior to the trial. Bacterial and yeast dermatitis or otitis was treated as appropriate and ectoparasite control was achieved with monthly application of a topical spot-on

(Stronghold®, Pfizer, Berlin, Germany). Long-term therapies, such as thyroxine supplementation or treatment for epilepsy, were continued throughout the trial if dogs had received these treatments for at least four weeks prior to the trial and they were not flavoured with proteins such as beef or pork.

2.2. Elimination diet

Each dog was fed a home-cooked elimination diet consisting of a mixture of a carbohydrate and a protein not previously fed or a commercial diet with hydrolysed proteins for 8–10 weeks. Details of the diet are given in Table 1. If the dogs improved on the diet, they were fed with the previous original diet for 10–14 days. There was intensive counselling of owners to ensure that no other food or food-flavoured supplements were administered during the diet trial. The owners used a diary to record defecation, pruritus or any gastrointestinal signs.

2.3. Evaluation of serum IgG and IgE antibodies

Blood samples for serologic testing were obtained before the diet trial and in dogs improving on the diet a second sample was taken directly at the end of trial. Fifty-seven specimens were obtained, 27 samples before and after diet and 3 samples after the rechallenge. Serum was separated by centrifugation and stored at –20 °C prior to analysis. Food allergen-specific IgG and IgE in canine sera were assessed by enzyme-linked immunosorbent assay (ELISA) at Avacta Animal Health, York, UK. Allergen-specific IgE and IgG against beef, pork, lamb, duck, chicken, turkey, wheat, soybean, barley, rice, potato, corn, oat, cows' milk, egg, and white fish were measured. Allergen-specific IgE and IgG against bean, deer and horse could not be measured, because ELISA testing for those antigens was not available for measurement.

2.3.1. Antisera

Polyclonal goat anti-dog IgG (gamma-specific)-peroxidase conjugate (Kirkegaard and Perry Laboratories [KPL], Gaithersburg, MD, USA) was used for the detection of IgG.

Monoclonal biotinylated anti-canine IgE (5.91; Bruce Hammerberg, North Carolina State University, Raleigh, USA) was used for the detection of IgE.

2.3.2. Allergen extracts

All allergen extracts were purchased from Greer Laboratories (Greer Laboratories, Lenoir, NC, USA), except duck extract which was purchased from Squarix Biotechnology (Squarix Biotechnology, Marl, Germany).

2.3.3. Food-specific IgE and IgG ELISAs

Levels of allergen-specific serum IgE and IgG antibodies were measured by ELISA using modified protocols of previously described assays (Bexley et al., 2009; Foster et al., 2003). Briefly, polystyrene microtitre plates were coated with food antigens (Greer Laboratories Inc., Lenoir, NC, USA) diluted in 0.05 M carbonate/bicarbonate buffer. Wells

Table 1

Age, gender, breed and utilised diets of dogs with AFRs.

Dog no.	Age	Gender	Breed	Utilised diet
1	<1	M	Mix	Hills z/d ultra dry food
2	6	M	Mix	Horse, potatoes
3	<1	FS	West Highland White Terrier	Royal canin, hypoallergenic dry food
4	<1	F	Giant Schnauzer	Royal canin, hypoallergenic dry food, horse
5	<1	M	French Bulldog	Royal canin, hypoallergenic dry food
6	2	F	West Highland White Terrier	Ostrich, Potatoes
7	<1	M	Beagle	Royal canin, hypoallergenic dry food
8	2	F	Labrador Retriever	Royal canin, hypoallergenic dry food
9	3	FS	Mix	Kangaroo, potatoes, buckwheat
10	1	MN	Golden Retriever	Horse, white beans
11	1	MN	West Highland White Terrier	Royal canin, hypoallergenic dry food
12	2	M	Tibet Terrier	Royal canin, sensitivity control dry food
13	5	M	Tibet Terrier	Horse, pOTATOES
14	4	M	Golden Retriever	Beans, potatoes
15	1	M	West Highland White Terrier	Deer, potatoes
16	10	FS	West Highland White Terrier	Horse, potatoes, beans
17	<1	FS	Doberman	Horse, potatoes
18	5	FS	Cocker Spaniel	Horse, potatoes
19	2	F	Boxer	Horse, potatoes

were then blocked with 0.2% fish gelatin. Samples were assayed in duplicate at dilutions of 1/10 (IgE) and 1/400 (IgG). Each plate contained a five-point standard curve prepared by assaying serial two-fold dilutions of a dog serum sample with high levels of beef-specific IgE or IgG, as appropriate. Food-specific serum IgE and IgG antibodies were detected using biotinylated monoclonal 5.91 (Bruce Hammerberg, North Carolina State University, Raleigh, NC, USA) and polyclonal goat anti-dog IgG peroxidase (Kirkegaard and Perry Laboratories, Gaithersburg, MD, USA), respectively. Absorbances were determined at 450 nm using an ELISA plate reader (Molecular Devices Co., Sunnyvale, CA, USA), with subtraction of mean blank (un-coated) well optical density (OD). Results were expressed as arbitrary units (AUs) by reference to the standard curve.

2.4. Statistics

Pre- and post-diet serum concentrations of allergens not fed during the elimination diet trial were compared with a Wilcoxon matched pairs test. In addition to comparing the antibody concentrations against individual allergens, scores for antibodies against all individual antigens were added up to form a total antibody score for each dog. The total scores before the diet and those after the diet were also compared with a Wilcoxon matched pairs test. IgE and IgG concentrations of dogs on a home-cooked diet were compared with those on a commercial diet with a Kruskal Wallis test and Dunn's post test. Graphpad Instat 3.01 (Graphpad, San Diego, CA, USA) was used and a two-tailed *P*-value of 0.05 was considered significant.

3. Results and discussion

3.1. Study objects

Of the 98 dogs initially included in this study, only 19 dogs were evaluated with complete data sets. In most of the other dogs, there was no improvement at all during the elimination diet, in some dogs owner compliance

prevented an evaluation, whilst in others it was impossible to obtain a complete set of blood samples. Fourteen of the dogs, who participated in this study showed a good response to the diet and in a further five dogs the response was questionable or only very subtle. Of the 14 dogs with a good response deterioration upon rechallenge was seen in seven dogs, in one dog the reaction was not clear, but the owner refused a further rechallenge after returning to the diet. In 6 dogs the owner refused to perform a rechallenge altogether and in the five dogs with no significant improvement during the elimination diet a provocation did not change the clinical signs. In addition, blood samples could only be obtained from three dogs after a positive rechallenge with the previous diet, because the owners of the other dogs either refused further sampling or lived a long way from the clinic, did not come back for a reevaluation, but were contacted by telephone instead and were thus lost to follow up.

The age, gender and breed of the dogs and the diets used are listed in Table 1.

3.2. Concentrations of serum food-specific IgE

IgE against duck, egg and white fish could not be detected, and only one dog had IgE against chicken and turkey, respectively. Only two of the blood samples contained IgE against wheat, soybean, barley, rice, potato, oat and corn; both were post-diet and from the same two dogs. None of these allergens were included in the statistical evaluation due to the low number of reactions. For the remaining allergens (beef, pork, lamb and milk), the mean IgE concentrations before and after the diet are listed in Table 2, the individual values in Table 3. There was no significant difference between the serum food specific antibodies before and after the diet for any of the individual allergens nor for the grouped IgE concentrations of all antigens ($P=0.55$). Similarly, there was no difference between the IgE concentrations of dogs on a commercial diet compared to those on a home-cooked diet.

Table 2

Mean ($\pm$ SD) serum IgE concentrations (in Arbitrary Units) against food antigens before and after an elimination diet in allergic dogs ($n = 19$) with AFRs.

	Pre-diet IgE concentrations	Pre-diet IgE concentrations	P-value comparing pre- and post-IgE concentrations (Wilcoxon matched pairs test)
Beef	2.37 $\pm$ 1.78	2.13 $\pm$ 1.6	0.67
Pork	0.53 $\pm$ 0.82	0.26 $\pm$ 0.42	0.26
Lamb	1.13 $\pm$ 1.46	1.05 $\pm$ 1.2	0.78
Cows' milk	1.84 $\pm$ 1.63	1.79 $\pm$ 1.8	0.92

3.3. Concentrations of serum food-specific IgG

IgG against white fish could not be detected, and only one dog had IgG against potato and egg, respectively. Only two of the blood samples contained IgG against wheat and barley, and four dogs reacted against soybean. None of these allergens were included in the statistical evaluation due to the low number of reactions. For the remaining allergens (beef, pork, lamb, milk, chicken and turkey), the IgG concentrations before and after the diet are listed in Table 4 and the individual concentrations of the four allergens against which antibodies were most commonly found, in Table 5. There was no significant difference between the serum food specific antibodies before and after the diet for any of the individual allergens nor for the grouped IgG concentrations of all antigens ($P = 0.53$). Similarly, there was no difference between the IgG concentrations of dogs on a commercial diet compared to those on a home-cooked diet.

Many authors describe specific IgE and IgG serum concentration for detection of AFRs as not acceptable. Testing with a polyclonal IgE antibody was not considered to be reproducible (Wilhelm and Favrot, 2005), and measurement of serum allergen-specific IgE to food allergens with a monoclonal ELISA test was reported unreliable

Table 4

Mean ($\pm$ SD) serum IgG concentrations (in Arbitrary Units) against food antigens before and after an elimination diet in allergic dogs ($n = 19$) with AFRs.

	Pre-diet IgG concentrations	Post-diet IgG concentrations	P-value comparing pre- and post-IgG concentrations (Wilcoxon matched pairs test)
Beef	1.76 $\pm$ 1.18	1.6 $\pm$ 1.1	0.66
Pork	0.66 $\pm$ 0.67	0.61 $\pm$ 0.51	0.79
Lamb	1.53 $\pm$ 0.75	1.5 $\pm$ 0.76	0.98
Cows' Milk	0.89 $\pm$ 1.08	0.76 $\pm$ 1	0.48
Chicken	0.26 $\pm$ 0.45	0.11 $\pm$ 0.31	0.23
Turkey	0.71 $\pm$ 0.65	0.66 $\pm$ 0.58	0.78

(Mueller and Tsohalis, 1998). Many food ingredients provoke antibodies (IgE and IgG) in patients who do not show any dermatological or gastrointestinal symptoms (Foster et al., 2003). However, a recent study showed a reasonable sensitivity and negative predictability of serum testing for food antigens and recommended the use of serum testing as a helpful tool to select an elimination diet (Schaefer et al., 2011). The current study was not designed to detect AFRs. The purpose was to evaluate the change in antibodies during an elimination diet where the patients were not exposed to the antigens tested. It would have been interesting to test the allergens fed during the elimination diet. Unfortunately there does not exist a serological test against bean, deer or horse to the authors' knowledge. One dog was fed a diet based on hydrolyzed soybean and showed a mild positive reaction after, but not before the diet, indicating that antibody production to soy may be possible whilst being fed a hydrolyzed soy diet. Few studies exist that evaluate the change in serum concentration of food specific antibodies depending on the offered diet (Jackson and Hammerberg, 2002; Jackson et al., 2003). In these studies, clinically relevant parameters could not be seen with changes of specific antibody serum

Table 3

Pre- and post-diet IgE antibody concentration in AU (arbitrary units) against selected food antigens in allergic dogs.

Dog no.	Beef-specific	Pork-specific	Lamb-specific	Milk-specific
	Pre IgE–post IgE	Pre IgE–post IgE	Pre IgE–post IgE	Pre IgE–post IgE
1	2–1.5	0–0.5	0–0.5	2–1
2	5–0	0–0	2–0	4–0
3	0–2	0–0	1–2	0–4
4	2.5–0.5	1–0	0.5–0	2–0.5
5	2–2.5	0.5–0	0.5–2	1–2
6	4–0	0–0	0–0	3–0
7	0–2	0–0	0–0	0–2
8	3–2.5	0–1	2–3.5	2–3.5
9	3–2	0.5–0	0–0	1.5–0
10	0–2	0–0	0–0	0–0
11	0–1	0–0.5	0–0.5	0–0
12	1–1	1–0	2–	0–1
13	4–0	1–0	1–0	2–0
14	5–4.5	2–1	5–0	5–4
15	5–4	3–0	4–3	5–5
16	2–1	0–1	0–1	2–0
17	1.5–4	0–0	1–1	1–4
18	4–3	1–1	2.5–1.5	3.5–3
19	1–5	0–0	0–2	1–4

Table 5

Pre- and post-diet IgG antibody concentration in AU (arbitrary units) against selected food antigens in allergic dogs.

Dog no.	Beef-specific	Pork-specific	Lamb-specific	Milk-specific
	Pre IgG–post IgG	Pre IgG–post IgG	Pre IgG–post IgG	Pre IgG–post IgG
1	1–1	0.5–0.5	2–0.5	0–0.5
2	1–1	0–0	1–2	0–1
3	1–1	1–1	1–1	0–0
4	1.5–0.5	1.5–0	2–0.5	1–0
5	1.5–2.5	0.5–1	2–2	1.5–1
6	1–5	0–0	0–2	0–4
7	0–1	0–0	0–1	0–0
8	2–2	0–1	1–1	0–0.5
9	1.5–2	1–1	2–3	1.5–0
10	1–1	2–0.5	2–1.5	0–1.5
11	2–1	1–1	3–2	1–0.5
12	4–0	1–1	1–1	0–2
13	5–2	1–0	2–1	2–0
14	3–2	0–1.5	2–1	4–1.5
15	2–2	0–1	1–3	2–1
16	1.5–1	0–1	1.5–1	0–0
17	2.5–3	0.5–0	1.5–2.5	1.5–0
18	1–0	0.5–1	2–1	1.5–1
19	1–1.5	2–0	2–1.5	1–0

concentration and concentrations could not be used to predict clinical hypersensitivity. Although we saw significant clinical improvement with the elimination diets and could measure food-specific IgE and IgG, the serum concentration of these antibodies did not change during the diet despite a lack of allergen exposure during that time. In most patients, a lack of response to an elimination diet is due to the fact that clinical signs are caused by environmental rather than food antigens. In some patients however, a lack of response to the diet may be due to a cross-reactivity of the dietary antigen with previously fed antigens rather than an absence of an adverse food reaction. Based on this study, serum test results for food specific antibodies are not changed by an elimination diet. This means that a clinician can choose the ingredients of a new elimination diet based on testing of serum obtained at the end of or during the first diet.

Many of the dogs participating in this study may have been dogs allergic to environmental allergens as well. Dogs with atopic dermatitis due to environmental allergens have higher serum concentrations of food specific IgE than healthy dogs and dogs with gastrointestinal disease (Foster et al., 2003; Halliwell et al., 2005). In many studies (White, 1986; Carlotti et al., 1990; Rosser, 1993; Harvey, 1993) a variable number of patients with AFRs had clinical signs of atopic dermatitis. A clinical differentiation between AD caused by food antigens and AD caused by environmental allergens is not possible (Picco et al., 2008; Favrot et al., 2010). Olivry et al. (2007) recommended that all dogs with atopic dermatitis should be assessed for the possible contribution of food antigens to their manifestations of AD. Clinical improvement of a dog with environmentally induced atopic dermatitis on an elimination diet may be due to either a change in the environmental load of the offending allergens or a concurrent AFR characterised by signs of clinical dermatitis resolving because of the diet or both. Currently, the role of IgE-mediated mediated hypersensitivity in canine AFRs has not been clearly established (Hillier and Griffin, 2001). Furthermore, variations in serum

concentration of food specific IgE and IgG can be measured even in clinically normal dogs independent of diet (Foster et al., 2003). In human medicine, antibody production against ingested foods is a universal phenomenon in both children and adults, and is not associated generally with hypersensitivity against the ingested antigen (Johannsson et al., 1984).

Alternatively, it could be possible that some dogs in this study had non-immunologically mediated AFRs such as food poisoning, pharmacological, metabolic reaction or idiosyncratic reactions (Hillier and Griffin, 2001). In these dogs, one would not expect a change in antibody concentrations with the positive clinical response to the exclusion diet. In humans, most of the AFRs are non-immunologically mediated (Sampson, 1999). In dogs, the prevalence and ratio of immunologically and non-immunologically mediated AFRs are unknown (Chesney, 2001).

In this study, some dogs showed very high high pre- and/or post-diet serum concentrations of food-specific antibodies, whilst in other dogs, no changes could be measured. However, the results of the serum concentration of food-specific antibodies did not correlate to changes in diet.

A variety of factors may influence antigen-specific serum IgE production. These include possible genetic variation within and between breeds, the type of antigen, and the dose, route, frequency and interval of administration and concurrent other hypersensitivities (Foster et al., 2003). The immune response may also be influenced by previous or concurrent gastrointestinal parasitic and microbial infections (Olsen et al., 2000). Furthermore, adjuvants administered with vaccines, and the vaccines themselves may influence the serological responses (HogenEsch et al., 2002; Tater and KC, 2005). Unfortunately, it was not recorded when the dogs participating in this study were vaccinated.

In conclusion, serum concentration of food-specific antibodies did not change during the elimination diet indicating that an elimination diet does not influence the results of serum testing for food-specific antigens.

4. Conflict of interest

This study was self-funded. Jennifer Bexley is employed by the laboratory running the IgE and IgG assays, but was not informed of the specimen details prior to running the assays.

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