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Food-specific serum IgE and IgG reactivity in dogs with and without skin disease: lack of correlation between laboratories

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Background – Despite conflicting data on their utility and no reports on interlaboratory reproducibility, serum food-specific antibodies are commonly assayed in first-opinion canine practice.

Hypothesis/Objectives – To determine both the variability of test results between two laboratories and the frequencies and magnitudes of food reactivity in dogs of different disease status.

Animals – Sera were obtained from eight dogs with cutaneous adverse food reaction (Group A), 22 with non-food-induced atopic dermatitis (Group B), 30 with an allergic/inflammatory phenotype (Group C), 12 with miscellaneous skin diseases (Group D) and nine healthy dogs (Group E).

Methods – Paired sera were submitted to two laboratories (A and B) for assays of food-specific IgE and IgG antibodies.

Results – Numbers of positive IgE and IgG tests determined by each laboratory in Groups A, B, D and E were comparable (Group C not included). Significant differences in the magnitude of IgE reactivity between groups for each allergen were seen only for lamb (Laboratory A, $P = 0.003$); lamb reactivity in Group D exceeded Group E ($P = 0.004$) but was comparable between all other groups. Agreement (kappa statistic) between the two laboratories' tests was 'moderate' for one antigen (potato IgE), 'fair' for four (corn IgE, rice IgE and IgG and soya bean IgG), 'slight' for eight (six IgE and two IgG) and 'less than chance' for the remaining six antigens (three IgE and three IgG).

Conclusions and clinical importance – These laboratories' tests appear to have dubious predictive clinical utility because they neither correlate nor distinguish between dogs of different disease status.

Introduction

Adverse food reaction (AFR) is a broad term used to describe any abnormal response to ingestion of a food or food additive.[1,2] Adverse food reactions encompass non-immune-mediated, intolerant reactions and immune-mediated, allergic responses, commonly mediated by IgE.[1–3] In dogs, the mechanisms of AFR are not well defined, although it has been suggested that they may reflect hypersensitivity responses of types one, three or four[4] or intolerance associated with enzyme deficiencies, abnormal absorption or naturally occurring chemicals in food.[5] An AFR principally manifesting with dermatological clinical signs is termed 'cutaneous adverse food reaction' (CAFR), but dogs may also present with gastrointestinal signs, with or without concurrent skin disease.[6–8] Cutaneous adverse food reaction may develop between the ages of 7 weeks and 13 years, often presenting with nonseasonal pruritus affecting the ears, feet, face, ventrum, limbs or perineal regions.[9–11] The true prevalence of adverse food reactions in the canine population is not known, although figures of between 7.6 and 12% have been reported amongst populations of dogs seen at dermatology referral centres.[12,13]

The 'gold standard' diagnostic test for CAFR, an elimination dietary trial followed by provocative exposure,[14] can be difficult and costly to perform, and is heavily reliant on owner and dog compliance. Laboratory or *in vivo* tests are therefore attractive alternatives, but intradermal tests with food antigens have shown poor predictive values and poor correlation with the results of dietary trials.[15,16] Recently, negative patch test responses with food allergens were shown to correlate well with tolerance in feeding trials with CAFR, but positive reactivity was less

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The names of the laboratories used in this study are available from the authors upon request.

helpful due to frequent false-positive reactions.[17] Unfortunately, patch tests are challenging to perform in a routine clinical environment. Serological tests measuring IgE are commonly used in human medicine, and tests measuring IgE and IgG to food antigens in dogs are readily available. Some investigators have suggested that these tests are of value in selecting allergens to avoid in a dietary trial.[17,18] Others have reported a poor correlation with clinical presentation and dietary trial results[19,20] and poor intra-assay reproducibility.[21] Despite these limitations, serological tests for food-specific serum antibodies are actively marketed to, and widely used in, first opinion veterinary practices in the UK. However, the authors' experiences match previous publications in that 'positive' results are common in dogs whose final diagnosis is not CAFR. Furthermore, some practitioners assume that a 'positive' test is diagnostic for CAFR and then erroneously cease investigations for alternative or concurrent diagnoses and/or unnecessarily instruct the owner to avoid food antigens identified in the test.

Given that the reproducibility of results of canine food-specific serological tests between laboratories does not appear to have been reported, we aimed to determine the variability of test results between two commercial laboratories by submission of paired sera to each. A further aim was to determine the frequency and magnitude of serological reactivity to foods in dogs with CAFR, other skin diseases, especially those that might resemble CAFR, such as nonfood-induced canine atopic dermatitis (NFIAD), and in healthy dogs, as a measure of clinical utility.

Materials and methods

Study participants

The study was approved by the Royal Veterinary College's (RVC's) Ethics and Welfare Committee, and written informed consent was obtained from each owner prior to inclusion. Dogs with skin disease were recruited from the RVC's Queen Mother Hospital for Animals. Healthy dogs owned by staff and student members of the College community were sampled during the course of a study approved by the UK Home Office. The dogs were divided into five groups based on their history, clinical signs and dermatological investigations appropriate to their presentation (Table 1). Clinical signs considered consistent with CAFR included pruritus (nonseasonal where the duration allowed this to be determined), recurrent microbial infections of the skin (e.g. pyoderma and *Malassezia* dermatitis) and/or recurrent unilateral or bilateral otitis externa.

Dogs presenting with clinical signs of inflammatory skin disease underwent a diagnostic investigation that included assessment for ectoparasitic infestation (skin scrapings, trichography, coat brushing and trial insecticidal or acaricidal therapy where indicated) and microbial skin infection (microscopy of cytological specimens, bacterial and fungal cultures, and trial antimicrobial therapy where indicated). Dogs with an allergic phenotype were fed an elimination diet as described below. Allergic dogs that failed to respond to the dietary trial but whose clinical signs were consistent with atopic dermatitis[22,23] were allocated to Group B, provided they also fulfilled the diagnostic criteria of Favrot *et al.*[24] for NFIAD with higher specificity (six or more criteria from set 1) and also had no history of gastrointestinal disease potentially associated with adverse food reaction. Dogs with an allergic or inflammatory skin or ear disease that did not match the criteria of Groups A and B, including dogs that did not complete a dietary trial correctly or with gastrointestinal signs potentially associated with adverse food reaction or were lost to follow up, were included in Group C; these dogs were retained in the study to enhance the assessment of test reproducibility. Dogs with cutaneous signs not consistent with CAFR underwent appropriate routine dermatological investigations without a dietary trial and were allocated to Group D. Healthy dogs with no history of skin or gastrointestinal disease were allocated to Group E. Serological test results were not considered in the final diagnosis of each case.

Dietary trials

Commercial hydrolysed diets were normally used to assess the response to dietary restriction, but other commercial or home-cooked diets comprising protein and carbohydrate components were used infrequently when preferred by the owner or when other commercial diets were not palatable. Conclusions about the efficacy of the dietary trial were made only when test diets were fed strictly for at least 6 weeks and normally 8 weeks, in line with current recommendations,[11,18,25] unless a significant clinical improvement was observed sooner. Ectoparasiticidal therapy was maintained through-

Table 1. Criteria used to allocate a group of 81 dogs whose sera were tested for food-specific IgE and IgG antibodies into five clinical groups

Group	Group characteristics
A – proven CAFR cases	Dogs with clinical signs potentially consistent with CAFR that responded to a strictly performed elimination dietary trial, relapsed upon rechallenge and improved again upon feeding the test diet
B – nonfood-induced canine atopic dermatitis	Dogs with an allergic phenotype (whose clinical signs were potentially consistent with CAFR but failed to improve with a strictly performed diet trial and failed to relapse upon rechallenge) and a final diagnosis of canine atopic dermatitis that also matched the criteria of Favrot *et al.*[24] with higher specificity (set 1, six or more criteria)
C – allergic/inflammatory skin or ear disease not matching the criteria for Group A or B	Dogs with dermatological signs potentially consistent with CAFR matching one or more of the following groups: • diagnosis of canine atopic dermatitis that did not match the criteria of Favrot *et al.*[24] (set 1, six or more criteria) • dogs that did not undergo a strictly performed elimination diet trial or whose dietary trial results could not be interpreted clearly • dogs with history of gastrointestinal signs that were associated with, or potentially associated with, adverse food reaction
D – clinical signs of skin disease not suggestive of CAFR or allergic disease	Dogs with a final diagnosis that is not normally attributable to CAFR
E – healthy control dogs	Dogs with no clinical signs of skin, gastrointestinal or any other disease

Abbreviation: CAFR, cutaneous adverse food reaction.

out test and challenge periods in each case, and antimicrobial treatments were also maintained in dogs prone to recurrent microbial skin infections. The dietary trial was followed by a purposeful rechallenge with the previous diet for 14 days (or fewer if signs relapsed)[26] to assess for any relapse of clinical signs. Dogs that improved during the dietary trial, showed significant deterioration in clinical signs within the rechallenge period and then improved again with reintroduction of the test diet were diagnosed with CAFR and allocated to Group A. Any concurrent gastrointestinal signs potentially attributable to adverse food reaction were recorded.

Blood sampling

Blood samples were collected from dogs from an appropriate peripheral vein. The serum was separated by centrifugation and frozen at −20°C until two paired aliquots of the one sample were submitted by post to the two test laboratories. Anti-inflammatory drug usage prior to sampling was recorded, but no attempt was made to withdraw topical or oral glucocorticoids or ciclosporin, in line with common practice,[27] product literature from Laboratory A and recently published guidelines from an evidenced-based systematic review.[28]

Serological testing

Testing by enzyme-linked immunosorbent assay was performed by each laboratory to measure IgE and IgG to food allergens. Laboratory A and Laboratory B both offered testing for the following allergens: beef, lamb, chicken, turkey, pork, egg, milk, soya bean, corn, wheat, rice, potato and oat. Additionally, Laboratory A offered testing for duck, barley, white fish and, latterly, rabbit, venison and salmon. Laboratory B offered testing for fish-mix (later replaced with white fish and blue fish), sugar beet, carrot, peanut, yeast (later withdrawn) and, latterly, venison and pea. Laboratory A reported results on a scale from 0 to 5, with 0 being negative and 1–5 being positive. Laboratory B reported results as 'negative', 'borderline', 'positive' or 'high positive'. For the purposes of the study, 'borderline' results were considered to be 'negative', because Laboratory B did not consider these to be 'positive'; the four categories were assigned numerical values for analyses (negative = 0, borderline = 1, positive = 2 and high positive = 3). The results were reported by the laboratories without information on the clinical status of each participant.

Statistics

Statistical analyses were performed using the SPSS version 20 (IBM UK Ltd, Portsmouth, UK) and UNISTAT version 3.0 (Unistat Ltd, London, UK) statistical software packages, with $P < 0.05$ for significance. The kappa statistic was used to assess the agreement between the serological test results for each allergen assessed by the two laboratories, where 1 is perfect agreement, 0 is exactly what would be expected by chance and negative values indicate agreement by less than chance.[29] Both the numbers of positive IgE or IgG reactions reported by each laboratory and the degree of reactivity (0–5 for Laboratory A and 0–3 for Laboratory B, as routinely reported to submitting veterinary surgeons) to the individual antigens were compared between Groups A, B, D and E using Kruskal–Wallis tests; *post hoc* comparisons were performed using Mann–Whitney *U*-tests with Holm–Bonferroni adjustments of the *P*-value when significant differences between groups were identified. Group C was omitted from these analyses, because it contained some dogs whose food reactivity was not determined or where gastrointestinal signs were potentially attributable to adverse food reaction.

The names of the laboratories are available from the authors upon request.

Results

Study participants

Eight-one dogs were recruited, comprising 22 entire males, 28 neutered males, six entire females and 25 neutered female dogs. Ages ranged from 1 to 10 years, with a mean of 4.41 years and a median of 4.0 years. Thirty-five breeds were represented, with the Labrador retriever being the most common (seven of 81, 8.6%). Of the 81 dogs, 38 completed a strictly performed dietary trial of at least 6 weeks; in 26 cases, the dietary trial lasted 8 weeks or longer; five completed a 6 week trial and seven completed a 7 week trial. One dog showed a dramatic improvement after a dietary trial lasting 3 weeks. Dietary trials that lasted 5 weeks without improvement ($n = 3$) were considered uninterpretable. Thirty-five dogs received a commercial hydrolysed diet [Purina Veterinary Diets HA Hypoallergenic Canine Formula (Nestle Purina, Horley, UK) $n = 28$; Prescription diet z/d canine ULTRA allergen-free (Hill's Pet Nutrition Ltd, Watford, UK) $n = 6$; and Anallergenic AN18 (Royal Canin, Chester, UK) $n = 1$], two were fed home-prepared limited-ingredient diets of fresh meats and potato, and one dog was fed a beef-based commercial diet based on previous observations of a beneficial effect. During the trial period, 18 of these dogs received imidacloprid/moxidectin spot-on treatment (Advocate; Bayer, Newbury, UK), either monthly ($n = 17$) or every 6 weeks ($n = 1$), 15 received monthly selamectin (Stronghold Spot-on Solution for Dogs; Zoetis UK Ltd, London, UK), four received fipronil (Frontline Spot-on Dog 10% w/v solution; Merial Animal Health Ltd, Harlow, UK), and one dog received both fipronil and imidacloprid/moxidectin monthly (alternating applications every 2 weeks).

Eight dogs (21.1%) fulfilled the diagnostic criteria for CAFR and were included in Group A [hydrolysed diet (Purina HA), $n = 5$; home-prepared diet, $n = 2$; and commercial beef-based diet, $n = 1$], whereas the remainder did not and were allocated to Group B or C. Five of the Group A dogs also had evidence of gastrointestinal signs potentially attributable to adverse food reaction, and three of these five had concurrent signs of NFIAD. Of the 22 dogs in Group B (NFIAD), 18 showed positive reactivity to environmental allergens on either intradermal ($n = 15$) or serological testing ($n = 2$) or both ($n = 1$), one had negative serological and intradermal tests, and three were not tested.

Thirty of the 81 dogs in the study (37.0%) with clinical signs potentially consistent with CAFR were included in Group C [dietary trial was not (appropriately) performed or could not be interpreted clearly ($n = 23$), gastrointestinal signs potentially associated with adverse food reaction ($n = 2$) or both ($n = 3$), final diagnoses of canine atopic dermatitis without matching the criteria of Favrot *et al.*[24] ($n = 2$)]. The 12 dogs that were allocated to Group D (14.8%) had parasitic infestations (sarcoptic mange, $n = 1$; juvenile-onset generalized demodicosis, $n = 1$) or other skin diseases [symmetrical lupoid onychitis ($n = 3$), sebaceous adenitis ($n = 2$), primary follicular cornification disorder, ($n = 2$), and one case each of pemphigus foliaceus, cyclic flank alopecia and acral lick granuloma due to orthopaedic disease].

Any administration of glucocorticoids and ciclosporin in the 6 weeks prior to sampling is recorded in Table 2. One dog in Group C had received an injection of methylprednisolone acetate 6 weeks prior to sampling, which exceeded the 28 day estimated optimal withdrawal time for this product.[28]

Table 2. Proportions of dogs exposed to anti-inflammatory drugs prior to serological testing for food-specific IgE and IgG antibodies

Product	Group A (n = 8) [n (%)]	Group B (n = 22) [n (%)]	Group C (n = 30) [n (%)]	Group D (n = 12) [n (%)]	Group E (n = 9)
Topical glucocorticoid (overall)	3 (37.5)	7 (31.8)	9 (30.0)	3 (25.0)	0
Ear preparation	1 (12.5)	6 (27.2)	8 (26.6)	1 (8.3)	0
Betamethasone gel	1 (12.5)	0	0	2 (16.6)	0
Hydrocortisone aceponate spray	1 (12.5)	1 (4.5)	1 (3.3)	0	0
Oral glucocorticoid (overall)	1 (12.5)	4 (18.1)	12 (40.0)	5 (41.6)	0
Daily P or MP	0	0	7 (23.3)	1 (8.3)	0
Alternate day P or MP	0	4 (18.1)	5 (16.6)	4 (33.3)	0
Alternate day D	1 (12.5)	0	0	0	0
Injectable glucocorticoid (overall)	0	0	1 (3.3)	1 (8.3)	0
Soluble dexamethasone	0	0	0	1 (8.3)	0
Methylprednisolone acetate	0	0	1 (3.3)	0	0
Ciclosporin	1 (12.5)	3 (13.6)	2 (6.6)	1 (8.3)	0

Administration [number of recipients (percentage of group)] of glucocorticoids or ciclosporin to dogs with proven cutaneous adverse food reaction (Group A), nonfood-induced canine atopic dermatitis (Group B), other allergic/inflammatory skin diseases (Group C), miscellaneous nonallergic dermatoses (Group D) and healthy dogs (Group E) within 6 weeks of sampling for measurement of food-specific IgE and IgG antibodies by two commercial laboratories.

Abbreviations: D, dexamethasone; MP, methylprednisolone; and P, prednisolone.

Serological testing for IgE antibodies to food antigens

Sera from 78 dogs were assayed by Laboratory A (insufficient volume, n = 3), and 78 samples were assayed by Laboratory B (insufficient volume, n = 3). Laboratory A reported at least one positive IgE reaction in four of seven (57%) Group A dogs, 14 of 21 (67%) Group B, 19 of 30 (63%) Group C, nine of 11 (82%) Group D and four of nine (44%) Group E dogs. Laboratory B reported at least one positive IgE reaction in four of seven (57%) Group A dogs, 13 of 21 (62%) Group B, 17 of 29 (59%) Group C, eight of 12 (67%) Group D and four of nine (44%) Group E dogs. Overall, positive test reactivity to each antigen tended to be distributed evenly across the five groups of dogs, and the number of positive IgE reactions in each dog reported by either laboratory did not vary significantly between the four groups evaluated (Laboratory A, P = 0.11; Laboratory B, P = 0.87; Table 3 and Table S1 in Supporting information).

Whilst none of the healthy (Group E) dogs tested positive to lamb, milk, oat, egg, wheat and pork using Laboratory A, the highest frequencies of IgE reactivity to those antigens were seen in Group D dogs, whose skin diseases would not normally be attributable to CAFR (Table S1 in Supporting information). Potato and barley reactivity determined by Laboratory A tended to be associated with an allergic phenotype (Groups A–C; potato, 3.3–28.6% and barley, 4.8–14.3%), but was absent in Group D and E dogs. Wheat reactivity determined by Laboratory B was absent in healthy dogs but was most frequent in Group B (NFIAD) dogs. However, comparisons of the magnitude of serological reactivity for each individual antigen between Groups A, B, D and E as determined by the two laboratories showed significant difference only for lamb from Laboratory A (P = 0.003). *Post hoc* analyses [P-value for significance by Holm–Bonferroni method <0.0083 (0.05/6)] showed that the reactivity in Group D exceeded (P = 0.004) that of Group E (healthy dogs), whereas other groups had comparable values.

Serological testing for IgG antibodies to food antigens

Sera from 78 dogs were assayed by Laboratory A (insufficient volume, n = 3), and 78 samples were assayed by Laboratory B (insufficient volume, n = 3). Laboratory A reported at least one positive IgG reaction in four of seven (57%) Group A dogs, 15 of 21 (71%) Group B, 20 of 30 (67%) Group C, seven of 11 (64%) Group D and six of nine (67%) Group E dogs. Laboratory B reported at least one positive IgG reaction in six of seven (86%) Group A dogs, 13 of 21 (62%) Group B, 19 of 29 (65%) Group C, nine of 12 (75%) Group D and eight of nine (89%) Group E dogs. There were no significant differences in the number of positive IgG reactions between groups as determined by Laboratory A (P = 0.54) and Laboratory B (P = 0.10; Table 3 and Table S2 in Supporting information).

Overall, where present, positive test reactivity to each antigen tended to be distributed evenly across the five groups of dogs (Table S2 in Supporting information). Laboratory A reported either frequent or infrequent positive IgG reactivity in all groups except Group A dogs (proven CAFR) for chicken, lamb, pork and rice, whereas infrequent corn reactivity was seen in all groups except Group E (healthy dogs). The magnitude of IgG reactivity reported by Laboratory A for each antigen tested did not vary significantly between the four groups of dogs that were tested.

Laboratory B reported positive IgG reactivity to wheat in all but one animal in Group A (proven CAFR) and all but one animal in Group E (healthy dogs), and reactivity to corn had a frequency of 29–67% in these two groups (Table S2 in Supporting information). Reactivity to soya bean and rice was also reported frequently in all groups by Laboratory B, whereas reactivity to other antigens was either infrequent (beef, sugar beet and turkey) or absent (blue fish, carrot, chicken, egg, fish mix, lamb, milk, oat, peanut, pork, venison, white fish and yeast). The degree of IgG reactivity reported by Laboratory B for each antigen tested did not vary significantly between the four groups of dogs that were tested.

Table 3. Comparison of total food-specific IgE and IgG reactivity as reported by two different laboratories

Test	Group A			Group B			Group C			Group D			Group E			*P*-value*
	Median	Range	Quartiles	Median	Range	Quartiles	Median	Range	Quartiles	Median	Range	Quartiles	Median	Range	Quartiles	
Laboratory A IgE	1	0–5	0, 4	2	0–8	0, 3	1	0–11	0, 3.5	3	0–8	2, 4	0	0–2	0, 2	0.11
Laboratory B IgE	1	0–5	0, 3	2	0–5	0, 3	1	0–6	0, 3	1	0–4	0, 2.8	0	0–5	0, 2.5	0.87
Laboratory A IgG	1	0–3	0, 2	2	0–9	0, 4	1	0–10	0, 3.3	1	0–9	0, 2	1	0–6	0, 5.5	0.54
Laboratory B IgG	2	0–5	2, 4	1	0–6	0, 3.5	1	0–7	0, 3	1.5	0–5	0.3, 2.8	4	0–5	2, 4.5	0.10

Number of positive reactions (median, range, lower and upper quartiles) to food allergens (per dog) in dogs with proven cutaneous adverse food reaction (Group A), nonfood-induced canine atopic dermatitis (Group B), other allergic/inflammatory skin disease (Group C), miscellaneous nonallergic dermatoses (Group D) and healthy dogs (Group E) as determined by commercial serological assays of food-specific IgE and IgG from two laboratories (Laboratories A and B).

*Comparison between groups (excluding Group C) using Kruskal–Wallis test.

Correlation of results for food-specific IgE assays between the two laboratories

Laboratory A reported common positive IgE reactivity to beef (51.3% of 78 sera), frequent reactivity to lamb (33.3%) and milk (32.1%), less frequent reactivity to corn (14.1%), salmon (12.5%, $n = 24$), oat (11.5%), turkey (10.3%), rice (10.3%), chicken (9%), pork (9%), rabbit (8.3%), soya bean (7.7%), potato (6.4%), barley (6.4%), egg (5.1%), venison (4.2%, $n = 24$), white fish (3.8%), wheat (3.8%) and no reactions to duck (Table S1 in Supporting information).

Laboratory B reported frequent positive IgE reactivity to rice (30.8% of 78 sera), soya bean (29.5%), corn (25.6%), wheat (23.1%) and potato (17.9%), less frequent reactivity to milk (7.7%), turkey (6.4%), beef (5.1%), pork (3.8%), fish mix (2.8%, $n = 72$), egg (2.6%), oat (2.6%) and lamb (1.3%), and no reactions to blue fish ($n = 6$), carrot, chicken, pea ($n = 6$), peanut ($n = 72$), sugar beet, venison ($n = 6$), white fish ($n = 6$) and yeast (Table S1 in Supporting information).

The level of agreement as assessed by the kappa (κ) statistic between the two laboratories ranged from 'moderate' ($\kappa = 0.41$–0.6) for potato, 'fair' ($\kappa = 0.21$–0.4) for corn and rice, 'slight' ($\kappa = 0$–0.2) for six antigens (beef, lamb, milk, soya bean, turkey and wheat), to by 'less than chance' ($\kappa < 0$) for three antigens (egg, oat and pork; Table S1 in Supporting information). The kappa statistic could not be calculated for chicken because all values were zero from Laboratory B.

Correlation of results for food-specific IgG assays between the two laboratories

Laboratory A reported common positive IgG reactivity to beef (43.6% of 78 sera), frequent reactivity to lamb (24.4%) and milk (23.1%), and less frequent reactivity to venison (16.7%, $n = 24$), corn (16.7%), chicken (15.4%), soya bean (15.4%), pork (14.1%), rice (12.8%), salmon (12.5%, $n = 24$), barley (9.0%), rabbit (8.3%, $n = 24$), oat (7.7%), white fish (7.7%), potato (7.7%), turkey (6.4%), egg (3.8%), wheat (3.8%) and duck (1.3%; Table S2 in Supporting information).

Laboratory B reported common positive IgG reactivity to wheat (64.1% of 78 sera), pea (50%, $n = 6$), and soya bean (48.7%), frequent reactivity to rice (37.2%) and corn (28.2%), less frequent reactivity to potato (9.0%), sugar beet (6.4%), turkey (1.3%) and beef (1.3%), and no reactions to blue fish ($n = 6$), carrot, chicken, egg, fish mix ($n = 72$), lamb, milk, oat, peanut ($n = 72$), pork, venison, white fish ($n = 6$) and yeast (Table S2 in Supporting information).

The level of agreement as assessed by the kappa statistic between the two laboratories ranged from 'fair' ($\kappa = 0.21$–0.4) for soya bean and rice through 'slight' for corn and wheat to by 'less than chance' ($\kappa < 0$) for beef, potato and turkey (Table S2 in Supporting information). The kappa statistic could not be calculated for six antigens (chicken, egg, lamb, milk, oat and pork) because all values from Laboratory B were zero.

Discussion

It is axiomatic that laboratory diagnostic tests used in veterinary medicine should generate reliable and

reproducible results that facilitate either the differentiation of healthy animals from those affected by the relevant disease(s) or the selection of appropriate therapeutic modalities. The use of serological tests for CAFR has long been controversial; studies highlighting their limitations first appeared in the veterinary literature >22 years ago.[19] The present study provides further data that call into question the clinical utility of two commercial tests in common usage for the diagnostic investigation of CAFR in dogs.

Food-specific serum IgE antibodies

It is generally accepted that, although the pathomechanisms underlying CAFR in dogs remain to be determined accurately, it is likely that hypersensitivity or intolerance processes are involved.[5,17–19,30,31] The presence of serum IgE antibodies in some affected dogs, as reported in the present and previous studies, supports the concept of allergic sensitization and immediate hypersensitivity in at least a proportion of dogs with CAFR.[32,33] Unfortunately, serological tests are not likely to yield useful results in cases of food intolerance because such responses are thought not to be mediated by serum antibodies. Although it has been suggested that food intolerance is more frequent in dogs than true hypersensitivity,[33] defining the relative frequencies might guide further decision-making about the utility of serological testing in veterinary practice. One of the important attributes of a carefully performed dietary restriction trial with subsequent provocative exposure is that CAFR may be detected irrespective of the underlying mechanism.

Antigen-specific IgE antibodies are of potential pathogenic significance in allergic disorders in view of their potential to mediate activation and degranulation of mast cells and basophils upon allergen exposure, and to facilitate allergen capture by dendritic cells that express high-affinity IgE receptors.[5] Unfortunately, the comparable frequency of positive IgE reactivity across groups indicates that the presence of food-specific IgE is widespread amongst dogs of differing disease status, including healthy dogs, and is not exclusive to dogs with CAFR. This phenomenon of 'asymptomatic hypersensitivity'[34] has been observed in multiple previous studies.[17,18,20,30] Foster and others[30] reported that the percentages of 40 normal dogs and 91 atopic dogs without proven CAFR that tested positive for IgE to a panel of 15 food antigens ranged from 42.5% (fish) to 100% (barley) and from 60.4% (chicken) to 92.3% (fish), respectively. Halliwell and others[18] reported that 11 of 24 normal dogs (45.8%) and 19 of 32 atopic dogs that failed to respond to dietary restriction (59%) had IgE reactivity to one or more food antigens. Bethlehem and others[17] reported that food-specific IgE reactivity was detected in seven of 63 (11.1%) tests in 11 healthy dogs, but in only 11 of 196 (5.6%) tests in 25 allergic dogs; subsequent provocative exposure with the relevant foods showed that two of 13 'positives' were true positive (15.4%), whereas the remaining 11 were false positives (84.6%). Antigen-specific IgE reactivity in dogs without clinical hypersensitivity might, in some cases, reflect the genetically programmed 'high IgE-responder' tendency that has been previously demonstrated in laboratory dogs[33,35–37] and in client-owned West Highland white terriers.[38,39]

The failure to detect differences in the magnitude of serum IgE reactivity between healthy dogs and dogs with CAFR in the present study might reflect the relatively small group sizes. Halliwell and others[18] reported that the mean rank of serum IgE levels in 22 dogs with CAFR significantly exceeded those of 24 healthy dogs for 11 of 19 food allergens. In contrast, the mean rank of IgE levels was comparable between healthy dogs and dogs with CAFR for five antigens, and values in healthy dogs exceeded those of dogs with CAFR for one antigen (casein). Also, in the same study, the mean ranks of IgE values in atopic dogs were either equivalent to (five food antigens) or exceeded (four food antigens) those of dogs with CAFR. Furthermore, concentrations of soy and corn-specific serum IgE could not be used to predict clinical hypersensitivity following allergen challenge in a group of 14 Maltese × beagle laboratory dogs that had spontaneously developed sensitization to corn and soy.[16] Taken together, the results of the present and previous studies provide compelling evidence that neither the presence nor the magnitude of serum IgE reactivity to food antigens measured by existing assays can be used to predict the disease status of an individual dog, regardless of whether it is healthy or shows an allergic phenotype.

Food-specific serum IgG antibodies

The pathogenic significance of IgG antibodies to food antigens in dogs has not yet been elucidated; the traditional view was that their detection merely reflects previous exposure and tolerance and not a specific food-related pathogenesis.[40,41] Immunoglobulin G testing is not currently recommended in human medicine as part of the investigation for an adverse food reaction, and there is currently no evidence to support its use.[1,42–44] Although homocytotropic/reaginic or complement-fixing subclasses of IgG have been defined in dogs and other species,[45] their significance in CAFR is not yet clear and, by way of comparison, evidence for a role of IgG subclasses in canine atopic dermatitis has been described as 'at best, circumstantial'.[46] Conflicting data on IgG levels have been reported in studies of adverse reaction to cow's milk in humans;[47] milk-specific IgG1 and IgG4 in atopic children have been elevated in some studies,[48–50] but IgG levels were comparable or reduced in relation to healthy control subjects in others.[51–53] Development of tolerance in patients formerly reactive to cow's milk was associated with increasing levels of β-lactoglobulin-specific IgG4 in one study[54] but not in another.[55] It is not known whether the anti-IgG reagents used by the laboratories in this study are specific for any particular IgG subclass(es).

In a study of IgG antibodies to 18 food antigens in dogs with CAFR, atopic dermatitis and healthy control dogs,[18] the authors concluded that IgG antibody levels were 'even more discriminatory' than IgE values, because the mean rank values for 12 of 18 antigens in dogs with CAFR exceeded those of normal dogs. Unfortunately, most sera yielded positive values for most antigens, and the relevance of these data was not assessed by allergen challenge. Furthermore, the mean rank values for food-specific IgG were comparable in dogs with atopic

dermatitis and CAFR for 14 of 18 antigens; differentiation between these two groups is of importance because they cannot be distinguished by clinical presentation alone.[18,24,56] Bethlehem and others[17] compared serological test results for food-specific IgG with dietary challenge in a challenge study and reported positive and negative predictive values of 34.8 and 83.7%, respectively; negative test results were more predictive than positive ones but did not appear sufficiently reliable for routine clinical use. Food-specific IgG antibodies in atopic dogs might reflect either dietary exposure or cross-reaction with environmental allergens, reflecting a general hyper-responsiveness of their immune system.[30] Given these uncertainties and, in particular, the relative paucity of studies comparing the results of individual food challenge in CAFR dogs with serum IgG reactivity, it is difficult to understand how a clinician can currently interpret the significance of a positive IgG result to a food antigen usefully.

Correlation between laboratories

The poor agreement between test results from the two laboratories seen for both IgG and IgE for all allergens tested is likely to have a significant impact on clinical decision-making in a practice environment. The frequencies of positive IgE test reactivity amongst the most commonly implicated antigens (beef, lamb and milk) from Laboratory A were four to 26 times higher than those of Laboratory B. The frequencies of positive IgE test reactivity amongst the most commonly implicated antigens (rice, soya, corn and wheat) from Laboratory B were 1.7 to six times higher than those of Laboratory A, and similar relations were observed for IgG reactions to those same antigens. These data are reflected in the low levels of agreement as determined by the kappa statistic; most of these comparisons showed values indicative of either slight agreement or agreement by less than chance. Clinicians relying on the results of one laboratory might inadvertently formulate the dietary trial to include particular food antigens based on negative results, when data from the other might indicate potential sensitivity to those same antigens. The frequencies of reactivity to wheat, soy, corn and rice (Laboratory B) and to lamb, corn and rice (Laboratory A) seem disproportionately high, whereas reactivity to wheat (Laboratory A) and to beef and chicken (Laboratory B) seem disproportionately low, when compared with a global review of the foods reported to cause CAFR in dogs based on direct challenge.[57] The lack of agreement between the results from the two laboratories presents a significant challenge to the credibility of the test results because it not clear which, if either, laboratory has provided a meaningful result.

In human medicine, studies of serum IgE tests for food and environmental antigens between different laboratories have shown similar variability, with the potential for serious implications for the diagnosis, management and treatment of patients with certain tests.[58–61] It is not clear whether the lack of correlation in the present study reflects the use of nonstandardized antigens from alternative sources, different anti-IgE and IgG reagents or other technical differences in the methodology.[33,59] A recent report described similar variability between four veterinary laboratories offering allergen-specific IgE assays for environmental allergens,[62] and poor intralaboratory reproducibility has also been reported.[63] The results of the present study support previous urgent calls for standardization and the application of independent systematic quality control approaches to veterinary laboratories offering tests of this nature.[63–65]

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Table S1. Comparison of the frequency of positive IgE serological test reactivity to food allergens, as reported by two different laboratories.

Table S2. Comparison of the frequency of positive IgG serological test reactivity to food allergens, as reported by two different laboratories.

Résumé

Contexte – Malgré des données conflictuelles sur leur utilité et aucun élément sur leur reproductibilité interlaboratoire, les anticorps sériques spécifiques alimentaires sont fréquemment dosés en première intention en pratique canine.

Hypothèses/Objectifs – Déterminer à la fois la variabilité des résultats des tests entre deux laboratoires et les fréquences et magnitudes de la réactivité alimentaire chez les chiens de différents statuts.

Sujets – Les sera ont été obtenus sur huit chiens présentant des lésions cutanées liées à une hypersensibilité alimentaire (Groupe A), 22 avec une dermatite atopique non liée à l'alimentation (Groupe B), 30 avec un phénotype allergique/inflammatoire (Groupe C), 12 avec diverses dermatoses (Groupe D) et neuf chiens sains (Groupe E).

Méthodes – Les sera par pair, ont été soumis à deux laboratoires (A et B) pour des dosages d'anticorps IgE et IgG spécifiques alimentaires.

Résultats – Les nombres de dosages IgG et IgE positifs par laboratoire pour les groupes A,B,D et E étaient comparables (Groupe C non inclus). Des différences significatives dans la magnitude de la réactivité d'IgE entre les groups pour chaque allergène étaient vus seulement pour l'agneau (Laboratoire A, $P = 0.003$); la réactivité de l'agneau du Groupe D dépassait le Groupe E ($P = 0.004$) mais était comparable entre tous les autres groups. La corrélation (statistique kappa) entre les tests des deux laboratoires étaient « modéré » pour un antigène (IgE pomme de terre), « faible » pour quatre (IgE de mais, IgG et IgE de riz et IgG de soja), « très faible » pour huit (six IgE et deux IgG) et « peu probable » pour le reste de six antigènes (trois IgE et trois IgG).

Conclusions et importance clinique – Ces tests de laboratoires semblent avoir une utilité prédictive douteuse car ils ne sont ni corrélés ni distinguable entre les chiens de différent statut sanitaire.

Resumen

Introducción – a pesar de los datos conflictivos acerca de su utilidad, y de que no existen informes de reproducibilidad entre laboratorios, los anticuerpos séricos específicos de alimentos son comúnmente ensayados en clínicas veterinarias caninas de primera opinión.

Hipótesis/Objetivos – determinar la variabilidad de las pruebas entre los laboratorios y la frecuencia y las magnitudes de reactividad a alimentos en perros con diferentes enfermedades de la piel.

Animales – se obtuvo suero de ocho perros con reacciones adversas cutáneos a alimentos (grupo A), 22 con dermatitis atópica no inducida por alimentos (grupo B), 30 con un fenotipo inflamatorio/alérgico (grupo C), 12 con enfermedades de la piel de otro tipo (grupo D), y nueve perros sanos (grupo E).

Métodos – se remitieron sueros pareados a dos laboratorios (A y B) para ensayos de la actividad específica alimentaria dada por producción de anticuerpos IgE a IgG.

Resultados – el número de pruebas positivas IgE e IgG determinado para cada laboratorio en los grupos A, B, D y E fue comparable (no se incluye el grupo C). Hubo diferencias significativas en la magnitud de la reactividad IgE entre los grupos para cada alérgeno sólo en el caso del cordero (laboratorio A, $P = 0{,}003$); la reactividad a cordero del grupo D excedió al grupo E ($P = 0{,}004$) pero fue comparable entre todos los otros grupos. El nivel de concordancia (kappa estadística) entre los dos laboratorios fue moderado para un antígeno (IgE frente a patata), medio para cuatro (IgE frente a maíz y arroz, IgG frente a arroz y soja), y leve para ocho (seis IgE y dos IgG) y menos que por casualidad para los restantes seis antígenos (tres IgE y tres IgG).

Conclusiones e importancia clínica – las pruebas de estos laboratorios parecen tener una utilidad predictiva clínica dudosa porque no se correlacionan ni distinguen entre los perros con diferentes enfermedades de la piel.

Zusammenfassung

Hintergrund – Trotz kontroversieller Daten über ihre Nützlichkeit und keinerlei Berichten über Reproduzierbarkeit zwischen den Laboratorien, werden futter-spezifische Antikörper im Serum häufig in der Allgemeinpraxis analysiert.

Hypothese/Ziele – Eine Bestimmung der Variabilität eines Testergebnisses zwischen zwei Laboratorien, sowie die Frequenz und das Ausmaß der Reaktion auf Futter bei Hunden in verschiedenen Krankheitsstadien.

Tiere – Es wurden Sera von acht Hunden mit einer kutanen Futtermittelunverträglichkeit (Gruppe A), von 22 Hunden mit nichtfutter-induzierter atopischer Dermatitis (Gruppe B), von 30 mit einem allergischen/entzündlichen Phänotyp (Gruppe C), von 12 mit unterschiedlichen Hauterkrankungen (Gruppe D) und von neun gesunden Hunden (Gruppe E) gewonnen.
Methoden – Gepaarte Sera wurden an zwei Laboratorien (A und B) zur Untersuchung von Futter-spezifischen IgE und IgG Antikörpern übermittelt.
Ergebnisse – Die Anzahl positiver IgE und IgG Tests durch jedes Labor in den Gruppen A, B, D und E waren vergleichbar (Gruppe C nicht inkludiert). Ein signifikanter Unterschied beim Ausmaß der Reaktivität von IgE zwischen den Gruppen für jedes Allergen wurde nur bei Lamm festgestellt (Labor A, $P = 0{,}003$); die Reaktivität auf Lamm übertraf in Gruppe D die Gruppe E ($P = 0{,}004$), war aber zwischen allen anderen Gruppen vergleichbar. Die Übereinstimmung (kappa Statistik) zwischen den Tests der beiden Labors war „moderate" für ein Allergen (Kartoffel IgE), „fair" für vier (Mais IgE, Reis IgE und IgG und Sojabohnen IgG), „slight" für acht (sechs IgE und zwei IgG) und „less than chance" für die übrigen sechs Antigene (drei IgE und drei IgG).
Schlussfolgerungen und klinische Bedeutung – Die Vorhersagbarkeit dieser Labortests zur klinischen Verwendung erscheint fraglich, da sie weder mit den verschiedenen Krankheitsphasen korrelieren, noch diese voneinander unterscheiden lassen.

要約

背景 – 有効性に関する対立するデータや研究機関間の再現性に関する報告がないにも関わらず、血清食物特異的抗体はイヌの診療において第１選択として一般的に測定されている。

仮説/目的 – 2つの研究機関間での検査結果のばらつきおよび異なる病気の状態のイヌにおける食物への反応の頻度と程度の両方を究明すること。

供与動物 – 8頭の皮膚食物有害反応を示すイヌ(グループA)、22頭の非食物誘発性アトピー性皮膚炎のイヌ(グループB)、30頭のアレルギー/炎症の表現型を示すイヌ(グループC)、12頭の様々な皮膚疾患を示すイヌ(グループD)ならびに9頭の健常犬(グループE)より血清を入手した。

方法 – 食物特異的IgEおよびIgG抗体の測定の為にペア血清を2つの研究機関(A、B)に提出した。

結果 – グループA、B、DならびにEでそれぞれの研究機関で測定したIgEおよびIgG検査陽性数は同等であった(グループCは含まれない)。グループ間でのそれぞれのアレルゲンに対するIgE反応性の程度における有意な差は羊肉に対してのみ(研究機関A、$P = 0.003$)みられた。グループDの羊肉反応性がグループEの反応性を超えていたが、他の全てのグループ間では同等であった。2つの研究機関の検査間の一致(κ統計量)は1つの抗原(じゃがいもIgE)に対して‘中等度’、4つの抗原(コーンIgE、米IgEおよびIgG、ならびに大豆IgG)に対して‘適度’、8つの抗原(6つのIgEおよび2つのIgG)に対して‘わずかな’、残りの6つの抗原(3つのIgEおよび3つのIgG)に対して‘偶然以下’であった。

結論および臨床的な重要性 – これらの研究機関の検査は異なった病気の程度のイヌの間で相関も区別もしなかったことから疑わしい予測臨床有効性を示した。

摘要

背景 – 尽管实践中有矛盾的数据，也没有不同实验室重复性的相关报告，检测血清特异性食物抗体仍是犬临床中的首选。

假设/目的 – 确定两个实验室测试的可变性和不同病情患犬的食物反应频率和大小。

动物 – 取8只食物副反应患犬（A组），22只没有食物副反应的异位性皮炎患犬（B组），具有过敏/炎性表型的30只犬（C组），12只其他皮肤病患犬（D组）和9只健康犬（E组）血清。

方法 – 成对的血清分别提交到两个实验室（A和B）去检测食物特异性IgE和IgG抗体。

结果 – 比较A、B、D、E组（C组除外）在每个实验室的IgE和IgG阳性数量。过敏原中只有羊肉IgE数值在各组中有显著差异(Laboratory A, $P = 0.003$)；羊肉反应D组超过了E组($P = 0.004$)；但与其余几组接近。两个化验室一致性（卡巴统计量）为：1个“中等”抗原（土豆IgE）、4个“一般”抗原（玉米IgE、米IgE和IgG、大豆IgG）、8个“轻微”抗原（六种IgE和2中IgG）、其余六种“少见”抗原（3种IgE和3种IgG）。

总结与临床意义 – 由于犬不同疾病的实验室检测既不相关也无区别，显然不具有确定的预测性临床价值。