Effect of an Omega-3/Omega-6 Fatty Acid-Containing Commercial Lamb and Rice Diet on Pruritus in Atopic Dogs: Results of a Single-Blinded Study

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ABSTRACT

A commercial, lamb and rice, dog food with an omega-6:omega-3 fatty acid ratio of 5.5:1 was fed in a single-blinded, self-controlled clinical trial to 18 atopic dogs. The pruritus in 8 of these dogs (44.4%) was satisfactorily controlled within 7 to 21 d, returned within 3 to 14 d after the diet was withdrawn, and was again controlled when the diet was reinstated. Plasma and skin levels of examined fatty acids changed in all 18 dogs when their diet was switched to the test diet. Dogs responding to the test diet had a different pattern of fatty acid change as compared to the dogs which failed to respond to the diet, suggesting that there are subsets of atopic dogs with different fatty acid metabolism capabilities.

RÉSUMÉ

Une ration commerciale pour chien à base d'agneau et de riz et ayant un ratio d'acides gras oméga-6 : oméga-3 de 5,5 : 1 fut utilisée dans une étude clinique réalisée à l'aveugle chez 18 chiens atopiques. Le prurit fut contrôlé de façon satisfaisante chez huit de ces chiens (44,4 %) à l'intérieur d'un délai de 7 à 21 jours, mais réapparu de 3 à 14 jours après le retrait de cette ration, et fut de nouveau contrôlé lorsqu'on recommença à donner cette ration. Les niveaux plasmatiques et cutanés des acides gras changèrent chez les 18 chiens lorsque leur diète fut modifiée pour la ration étudiée. Les chiens chez qui on nota une réponse au changement de diète avaient un schéma de changement d'acides gras différent de celui des chiens chez qui on ne nota pas de changement, ce qui suggère qu'il y a des sous-populations de chiens atopiques ayant des capacités différentes de métaboliser les acides gras.

(Traduit par docteur Serge Messier)

INTRODUCTION

Pruritus associated with hypersensitivity (allergy) reactions is the most common reason for dogs being presented to a veterinarian for dermatological diagnosis (1). After flea bite hypersensitivity, atopy is the most common allergic dermatosis of the dog (2–11).

Clinical management of canine atopy typically involves avoidance and the use of immunotherapy (hyposensitization), glucocorticoids, antihistamines, omega-3/omega-6 fatty acid-containing supplements, various topical agents, or combinations of these (2,3,12). Due to the ease of administration and safety attending their use in dogs, omega-3/omega-6 fatty acid-containing supplements have become quite popular for the treatment of canine atopic pruritus (1,12–17). Open clinical trials have indicated that the administration of these supplements to atopic dogs can result in satisfactory control of pruritus in 11.1% to 26.7% of the dogs (18–20); an approximate 50% reduction in pruritus in another 11.1% to 17.2% of the dogs (18,19); a 24% to 100% reduction in required glucocorticoid doses in some dogs (1,12,21,22); and a synergistic action with antihistamines in other dogs (1,12,20,23).

Two of the authors (DWS, WHM) were approached by a pet food manufacturer because of anecdotal observations by veterinarians in private practice that one of the manufacturer's commercial dog foods seemed to be beneficial for reducing pruritus in some allergic dogs. Analysis of the diet in question had revealed that it contained relatively large quantities of omega-3 and omega-6 fatty acids. The authors hypothesized that the omega-3/omega-6 fatty acid content of the food might be responsible for the food's purported antipruritic effects.

The purpose of this paper is to report the results of a single-blinded study on the effect of an omega-3/omega-6 fatty acid-containing commercial lamb and rice diet on pruritus in atopic dogs. In addition, fatty acid levels in the plasma and skin of these dogs were determined prior to the feeding of the diet, and again after the diet had been consumed for 8 wk.

MATERIALS AND METHODS

Eighteen dogs were randomly enrolled in the study as they were examined at the Small Animal Clinic of the College of Veterinary Medicine and their owners agreed to the protocol. The dogs represented several breeds, included 11 females and 7 males, varied in age from 2.0 to 12.0 y, and weighed from 6.0 to 41.5 kg (Table I). All dogs, except Case 15, had been consuming commercial dog foods that met or exceeded the National Research Council's requirements for complete canine nutrition. Case 15 was being fed a home-prepared lamb and rice diet. All dogs were diagnosed atopic, based on their classical history and physical findings; their failure to respond to a 4-to-6-week, home-prepared,

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TABLE I. Clinical data on 18 atopic dogs receiving the test diet

Case number	Breed	Sex	Age (y)	Weight (kg)	Duration of disease (y)	Number of positive skin test reactions	Type of dog food*	Response to test diet†
1	Boxer	FS	3	24	2	27	S	E
2	Toy poodle	MC	5	6	2	15	P	G
3	English springer spaniel	FS	4.5	16.4	3	7	P	E
4	West Highland white terrier	F	5	8	3.5	12	P	E
5	Basset hound	F	5	21	2	10	P	P
6	Labrador retriever	FS	2.5	29	1.5	1	P	E
7	Mongrel	MC	12	21	>3	4	P	P
8	Scottish terrier	MC	7	12	4	14	S	E
9	Dachshund	FS	8	6.6	2	16	P	P
10	West Highland white terrier	FS	6	6	1	12	P	G
11	Boxer	F	3.5	23	2	3	S	E
12	Labrador retriever	MC	2	35.7	1	17‡	NS	F
13	Labrador retriever	MC	4	41.5	2.5	4‡	NS	P
14	Chinese Shar Pei	FS	2	16.4	1	17‡	S	P
15	Golden retriever	F	3.5	26.4	2.5	17	H	P
16	Dachshund	MC	4	16.4	3.5	5‡	P	P
17	English springer spaniel	MC	5	26	3	5‡	S	P
18	Mongrel	FS	5	12	3.5	11	S	P

FS = spayed female; MC = castrated male
* S = standard commercial; P = premium commercial; H = homecooked; NS = not specified
† E = excellent; G = good; F = fair; P = poor
‡ Positive reaction to flea antigen

hypoallergenic diet (lamb or fish with potatoes or rice); and their positive reactions to intradermal skin tests (Table I). All dogs had nonseasonal pruritus and were free of bacterial pyoderma, *Malassezia* dermatitis, and ectoparasites, based on physical examination, cytology, and negative skin scrapings. The pruritus of all dogs was known to disappear completely to anti-inflammatory doses of glucocorticoids. No dog had received glucocorticoids for at least 4 wk prior to examination at the clinic.

Eleven dogs (cases 1–8,11,16,18) had received prior treatment with a commercial omega-3/omega-6 fatty acid-containing product (DVM Derm Caps, DVM Pharmaceuticals, Miami, Florida, USA) at the manufacturer's recommended dosage for 3 to 6 wk. None of the dogs had had any reduction in their pruritus during this treatment. No dog had received any fatty acid-containing products for at least 6 wk prior to examination at the clinic. All dogs were moderately to severely pruritic at examination.

Prior to the feeding of the test diet, all dogs had blood and skin samples taken for fatty acid profile analysis. Blood was collected in EDTA containing tubes, which were immediately centrifuged. The plasma was harvested immediately, placed in 2.5 mL plastic cryovials (Nalge Company, Rochester, New York, USA), and stored at −70°C until shipped on dry ice by overnight express mail to the laboratory (The IAMS Company, Lewisburg, Ohio, USA) for analysis. Fatty acid profile analysis was performed by capillary gas chromatography (24,25). A 6 mm full-thickness skin specimen was obtained by biopsy punch from clinically normal skin over the dorsolateral thorax, placed in 1.0 mL plastic cryovials (Nalge Company), frozen immediately, and stored at −70°C until shipped on dry ice by overnight express mail to the laboratory. Each biopsy included pannicular fat, but no attempt was made to standardize the amount taken. Prior to the skin biopsy specimens being obtained, the hair was gently removed by clipping, and the site was anesthetized by the subcutaneous injection of 2% lidocaine hydrochloride; no surface cleaning or other preparation was done. Samples were processed by the laboratory. Fatty acid profile analysis was performed by capillary gas chromatography (25).

All owners were instructed to feed only the test diet (Eukanuba Natural Lamb & Rice, The IAMS Company), which was supplied in 22.7 kg, unmarked, brown paper bags, for the subsequent 8 wk. Owners were asked to evaluate the reduction in the degree of pruritus experienced by their pets. Responses were classified as poor (0 to 25% reduction in pruritus), fair (26% to 50%), good (51% to 75%), and excellent (76% to 100%). No other treatments, other than control measures for pre-existing fleas, were allowed.

After 8 wk of being fed the test diet, and before the test diet was discontinued, the dogs were re-examined at the clinic. Blood and skin specimens were again obtained and submitted for fatty acid profile analysis, as described above. At this time, the owners were asked to bring in a sample of their dog's previous dog food in plastic bags (Whirl-pak, Nalge Company), which were then shipped on dry ice by overnight express mail to the laboratory for fatty acid profile analysis (25). Commercial foods were classified as standard, if they were available in grocery stores. The "premium" designation was used for foods available only through pet food stores, veterinarians, kennels, etc.

To estimate what impact fatty acid supplements would have on a dog's total daily fatty acid intake, dietary levels were converted from mg/kg of food to mg/kg of body weight/day. Based on the test diet manufacturer's recommendations, the dietary levels of the test diet were divided by 69.4 to compute the mg/kg BW/day. This factor was also used for all other diets.

If a dog had achieved a poor or fair response to the test diet, the study was terminated. The owners of these dogs were asked to report if their dog's pruritus worsened when they were returned to their original diet. Dogs

with a good or excellent response to the test diet were returned to their original diet for 3 wk or until pruritus returned. If pruritus did, indeed, return, the dogs were again fed the test diet for an additional 6 wk to determine whether or not the control of pruritus was reproducible.

The chi-square test of association was used to determine if response to the test diet was associated with sex, skin test reactivity, or positive skin test reactivity to flea antigen. The 2-sample *t*-test (26) was used to evaluate the influence of age and duration of disease on responsiveness to the test diet. The paired *t*-test was also used to analyze the differences among the standard and premium commercial foods, the pre-trial diets of the dogs that had been previously treated with a commercial fatty acid supplement, and the fatty acid profiles of the diet, plasma, and skin. A value of $P < 0.05$ was considered significant in all tests.

Pearson correlation matrices (26) were computed for the responders and nonresponders. Matrices comparing omega-6 fatty acid dietary change to omega-6 plasma change, omega-6 plasma change to omega-6 skin change, omega-3 dietary change to omega-3 plasma change, and omega-3 plasma change to omega-3 skin change were computed. Correlation coefficients of 0.8 or greater were considered indicative of excellent correlation.

RESULTS

The palatability of the test diet was excellent and no adverse reactions were reported. Eight of the 18 dogs (44.4%) had a good ($n = 2$) or excellent ($n = 6$) response during the initial 8- week period (Table I). Reduction in pruritus was appreciated within 7 to 21 d of the initiation of the test diet. When these 8 dogs were returned to their previous diet, pruritus returned within 3 to 14 d. Reinstitution of the test diet again resulted in good or excellent reduction of the pruritus. These 8 dogs have been maintained on the test diet and continue to do well during follow-up periods of 1.75 to 2.25 y. None of the owners of the dogs with a poor or fair response to the test diet noted any real difference in their dog's pruritus when its original food was given.

TABLE II. Mean* amounts (mg/kg of diet) of selected fatty acids in the test diet and the pre-trial diets of 18 atopic dogs and the mean percentage dietary change associated with feeding the test diet

		Pretrial diet levels		Percentage change associated with feeding the diet	
Fatty acid	Test diet	Responders	Nonresponders	Responders	Nonresponders
LA	16945.6	23240. ± 14230.	23290. ± 13060.	−0.931 ± 60.1[f]	34.7 ± 155.4[f]
GLA	1059.1	154.2 ± 81.0	146.1 ± 101.0	756.5 ± 426.9[g]	1220.3 ±1280.9[g]
DGLA	151.3	122.4 ± 57.3	123.3 ± 66.0	46.4 ± 61.5[h]	115.4 ± 240.2[h]
AA	605.2	316.7 ± 185.3	343.7 ± 214.9	167.7 ± 165.9[i]	334.8 ± 602.3[i]
DTA	151.3	87.7 ± 49.9	92.6 ± 54.8	128.5 ± 122.4[j]	351.0 ± 723.9[j]
AL	907.8	898.1 ± 262.9[a]	1600.6 ± 1505.8[a]	11.0 ± 41.4[k]	35.1 ± 162.5[k]
EPA	605.2	18.0 ± 7.1[b]	20.42 ± 13.87[b]	3699.0 ± 1335.0[l]	4494.7 ± 3040.4[l]
DPA	151.3	71.0 ± 80.8[c]	61.07 ± 38.58[c]	172.5 ± 106.7[m]	369.6 ± 554.2[m]
DHA	907.8	42.5 ± 28.1[d]	62.37 ± 54.93[d]	2866.0 ± 1577.6	1734.7 ± 1340.0
TO6	19215.1	24160. ± 14220.	24220. ± 13490.	5.4 ± 59.8[n]	47.6 ± 171.7[n]
TO3	3479.9	1054.5 ± 339.6[e]	1769.3 ± 1590.5[e]	264.6 ± 132.8[o]	360.3 ± 563.1[o]
TO6:3	5.5	21.9 ± 6.8	16.4 ± 4.4	−71.9 ± 11.2	−63.1 ± 14.6

LA = linoleic acid; GLA = γ-linolenic acid; DGLA = dihomo-γ-linolenic acid; AA = arachidonic acid; DTA = docosatetraenoic acid; AL = α-linolenic acid; EPA = eicosapentaenoic acid; DPA = docosapentaenoic acid; DHA = docosahexaenoic acid; TO6 = total omega-6 fatty acid content; TO3 = total omega-3 fatty acid content; TO6:3 = ratio of TO6 to TO3

* ± standard deviation; Values with the same superscript are significantly different

There was no significant influence of sex, skin test reactivity (≤ 10 vs > 10 positive intradermal skin test reactions), or duration of disease on responsiveness to the diet. There was no correlation of age with the number of positive intradermal skin test reactions. The dog's age and reactivity to flea antigen were significant. Older dogs (5.05 ± 2.99 y vs. 4.56 ± 1.52 y) ($P = 0.045$) and those positive to flea antigen ($P = 0.036$) were more likely not to respond to the test diet.

The standard diet of 15 dogs was available for fatty acid profile analysis and the mean values for selected fatty acids are shown in Table II. The profile of the test diet is also shown in this table. The levels of the fatty acids present varied greatly from diet to diet. When the regular diet of the good or excellent responders was compared with the regular diet of the nonresponders, there was no significant difference for linoleic acid (LA), γ-linolenic aid (GLA), dihomo-γ-linolenic acid (DGLA), arachidonic acid (AA), docosatetraenoic acid (DTA), total omega-6 content (TO6), and omega-6:omega-3 (TO6:3) ratio. The responders had statistically significant lower levels of α-linolenic acid (AL) ($P = 0.0001$) and total omega-3 content (TO3) ($P = 0.0003$) and higher levels of docosapentaenoic acid (DPA) ($P = 0.046$) in their regular diets compared with the levels in the nonresponders' diets. Levels of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were significant at $P = 0.052$ and were lower in the regular diet of the responders.

The percentage change in the dietary fatty acid levels resulting from the switch to the test diet are shown in Table II. Aside from a slight group mean decrease in linoleic acid among the responders, the switch to the test diet resulted in group mean increases in all the fatty acids studied. There was no significant difference between the responders and nonresponders for DHA or TO6:3. Responders had statistically significant lower percentage change of LA ($P = 0.0122$), GLA ($P = 0.0052$), DGLA ($P = 0.0011$), AA ($P = 0.0017$), DTA ($P = 0.0001$), AL ($P = 0.0010$), EPA ($P = 0.0242$), DPA ($P = 0.0004$), TO6 ($P = 0.0068$), and TO3 ($P = 0.0006$).

Commercial omega-3/omega-6 fatty acid supplements typically contain one or more of the following fatty acids: LA, GLA, AL, EPA, and DHA. Levels of these fatty acids in mg/kg BW/day for the test diet, the standard and premium commercial pre-trial diets of the dogs, and the pre-trial diets of the dogs previously treated with a commercial fatty acid supplement are shown in Table III. Levels for dogs that did or did not respond to the test diet are also shown. The fatty acid levels of individual foods within either the standard or premium groupings varied greatly, but the only

TABLE III. Mean* daily consumption (mg/kg of body weight/day) of selected fatty acid in the test diet, standard and premium commercial foods, and pretrial diets of dogs who failed to respond to commercial fatty acid supplement

	LA	GLA	AL	EPA	DHA	TO3
Test	244.1	15.3	13.1	8.7	13.1	50.13
Standard commercial food						
All dogs (n = 5)	213.6 ± 86.9	2.42 ± 1.26	10.05 ± 2.60[a]	0.26 ± 0.14	0.43 ± 0.25	11.5 ± 2.8[b]
Responders (n = 3)	216.2 ± 105.2	2.23 ± 0.48[c]	9.88 ± 2.97	0.23 ± 0.07	0.33 ± 0.11	11.2 ± 3.01
Nonresponders (n = 2)	209.7 ± 89.8	2.70 ± 2.37[c]	10.30 ± 3.03	0.30 ± 0.52	0.57 ± 0.40	12.0 ± 3.62
Premium commercial food						
All dogs (n = 8)	425.6 ± 180.8	2.09 ± 1.26	23.14 ± 18.67[a]	0.30 ± 0.17	1.02 ± 0.69	26.1 ± 19.4[b]
Responders (n = 5)	405.9 ± 226.1	2.21 ± 1.51	14.78 ± 3.07[d]	0.27 ± 0.12	0.78 ± 0.43	17.6 ± 4.31[c]
Nonresponders (n = 3)	458.4 ± 97.6	1.88 ± 0.94	37.08 ± 27.10[d]	0.35 ± 0.26	1.42 ± 0.94	40.4 ± 28.1[c]
Supplement failures						
All dogs (n = 9)	322.8 ± 145.1	2.30 ± 1.10	19.14 ± 18.7	0.29 ± 0.16	0.78 ± 0.71	21.3 ± 19.7
Responders (n = 7)	273.0 ± 115.5	2.41 ± 1.12	12.22 ± 3.45[f]	0.27 ± 0.11[g]	0.50 ± 0.28[h]	14.0 ± 3.8[i]
Nonresponders (n = 2)	497.2 ± 100.1	1.93 ± 1.32	43.38 ± 24.8[f]	0.36 ± 0.37[g]	1.76 ± 1.04[h]	47.0 ± 36.3[i]

LA = linoleic acid; GLA = γ-linolenic acid; AL = α-linolenic acid; EPA = eicosapentaenoic acid; TO3 = total omega-3 fatty acid content; DHA = docosahexaenoic acid

* ± standard deviation; Values with the same superscript are significantly different

TABLE IV. Mean* plasma levels (μg/mL of plasma) of selected fatty acids in 18 atopic dogs before and after the food trial

	Pretrial levels		Post-trial levels		Percentage change in plasma levels after dietary change	
Fatty acid	Responders	Nonresponders	Responders	Nonresponders	Responders	Nonresponders
LA	418.9 ± 140.2	456.4 ± 183.3	593.7 ± 85.4[c]	538.6 ± 167.6[c]	61.4 ± 77.2[e]	24.3 ± 40.1[e]
GLA	10.5 ± 4.8	10.5 ± 3.0	12.1 ± 3.5	11.9 ± 4.0	53.9 ± 63.2	9.1 ± 35.0
DGLA	7.4 ± 2.9	10.3 ± 4.3	10.8 ± 3.2	11.0 ± 2.6	60.2 ± 60.4[f]	16.6 ± 31.5[f]
AA	135.7 ± 61.7	154.7 ± 49.0	157.7 ± 60.5	168.3 ± 75.9	21.7 ± 27.7[g]	23.2 ± 67.9[g]
DTA	7.2 ± 4.3[a]	5.7 ± 1.9[a]	3.7 ± 1.4	4.1 ± 1.8	−35.1 ± 33.1	−13.5 ± 58.7
AL	3.8 ± 1.3[b]	5.7 ± 6.2[b]	9.1 ± 5.0[d]	6.3 ± 2.4[d]	162.1 ± 179.3[h]	47.5 ± 54.0[h]
EPA	6.00 ± 4.8	4.8 ± 4.1	25.4 ± 13.0	17.6 ± 8.2	537.1 ± 437.2	396.6 ± 338.8
DPA	5.8 ± 2.1	7.1 ± 2.9	12.3 ± 2.8	13.6 ± 3.9	134.4 ± 86.8	110.4 ± 72.6
DHA	7.8 ± 8.1	9.6 ± 7.8	24.6 ± 5.9	30.7 ± 10.6	702.5 ± 840.0	623.9 ± 878.5
TO6	586.1 ± 198.7	643.2 ± 225.5	785.6 ± 126.8	738.5 ± 167.7	49.7 ± 61.0	21.8 ± 37.1
TO3	24.4 ± 12.2	28.8 ± 15.3	73.5 ± 20.0	70.2 ± 22.5	274.1 ± 196.2	190.7 ± 158.3
TO6:3	29.2 ± 12.7	24.5 ± 12.8	11.0 ± 1.8	11.0 ± 2.2	−41.0 ± 63.5[i]	−50.8 ± 25.9[i]

LA = linoleic acid; GLA = γ-linolenic acid; DGLA = dihomo-γ-linolenic acid; AA = arachidonic acid; DTA = docosatetraenoic acid; AL = α-linolenic acid; EPA = eicosapentaenoic acid; DPA = docosapentaenoic acid; DHA = docosahexaenoic acid; TO6 = total omega-6 fatty acid contant; TO3 = total omega-3 fatty acid contant; TO6:3 = ratio of TO6 to TO3

* ± standard deviation; Values with the same superscript are significantly different

significant difference among the groups for LA, GLA, AL, EPA, DHA, or TO3 was in their omega-3 content. Premium foods had significantly greater amounts of AL (P = 0.0009), DPA (P = 0.0140), and TO3 content (P = 0.0010). In the standard food group, the only significant difference between the responders and nonresponders was in the GLA content, where nonresponders had higher levels (P = 0.0390). In the premium food group, significant differences were noted in AL and TO3, with nonresponders having higher levels of AL (P = 0.0006) and TO3 (P = 0.0020). No significant differences were detected in the fatty acid content of the diets of the responders that ate either a standard or a premium or the diets of the nonresponders that ate a standard or a premium food. Nine dogs had previously been treated with a commercial fatty acid supplement. Their pre-trial diets differed significantly in their omega-3 content. Dogs that failed to respond to the supplement and the trial diet had higher levels of AL (P = 0.0001), EPA (P = 0.0138), DHA (P = 0.0093), and TO3 (P = 0.0006).

In most instances, the pre-trial plasma (Table IV) or skin (Table V) fatty acid concentrations of the responders or nonresponders were not statistically different. Responders had significantly higher pre-trial plasma levels of DTA (P = 0.014) and lower levels of AL (P = 0.0002) compared with the nonresponders. Responders had significantly higher pre-trial skin levels of AA (P = 0.0054) and DTA (P = 0.0341) as compared with the nonresponders.

After the 8-week dietary trial, plasma fatty acid concentrations changed in all dogs, with a near uniform trend towards increasing levels (Table IV). With the exception of a decrease in the group mean percentage change for DTA, the dietary change resulted in increased group mean levels of all other fatty acids. In most instances, the post-trial plasma fatty acid concentrations of the responders or nonresponders were not statistically different. Responders had significantly higher post-trial levels of LA (P = 0.0447) and AL (P = 0.021) compared with the nonresponders. There was no statistical difference in the group mean percentage change for GLA, DTA, EPA, DPA, DHA, TO6, and TO3. The difference for GLA approached significance (P = 0.0511). Responders had a significant greater percentage increase in LA (P = 0.0361), DGLA (P = 0.0368), AL (P = 0.0009) and TO6:3 (P = 0.0079) compared with the nonresponders. Nonresponders had a statistically significant greater

TABLE V. Mean skin levels* of selected fatty acids in 18 atopic dogs before and after the food trial

Fatty acid	Pretrial levels		Post-trial levels		Percentage change in skin levels after dietary change	
	Responders	Nonresponders	Responders	Nonresponders	Responders	Nonresponders
LA	10.9 ± 5.3	15.3 ± 3.6	18.1 ± 8.6	16.4 ± 9.3	53.5 ± 75.2	14.9 ± 65.3
GLA	0.50 ± 0.05	0.01 ± 0.03	0.08 ± 0.12	0.07 ± 0.08	50.0 ± 129.1.	
DGLA	0.11 ± 0.06	0.08 ± 0.04	0.11 ± 0.06[c]	0.18 ± 0.19[c]	−7.1 ± 60.7[f]	100.0 ± 213.8[f]
AA	0.34 ± 0.31[a]	0.25 ± 0.13[a]	0.43 ± 0.32	0.57 ± 0.57	22.2 ± 40.4[g]	166.3 ± 258.9[g]
DTA	0.16 ± 0.09[b]	0.10 ± 0.05[b]	0.15 ± 0.09[d]	0.20 ± 0.19[d]	−9.5 ± 48.0[h]	9.44 ± 203.8[h]
AL	0.36 ± 0.18	0.50 ± 0.23	0.63 ± 0.28[e]	1.3 ± 2.4[e]	68.3 ± 88.3[i]	113.1 ± 244.2[i]
EPA	0.01 ± 0.04	0.01 ± 0.03	0.06 ± 0.07	0.03 ± 0.09		
DPA	0.14 ± 0.09	0.12 ± 0.08	0.21 ± 0.12	0.24 ± 0.34	61.9 ± 111.3[j]	124.1 ± 368.3[j]
DHA	0.06 ± 0.09	0.07 ± 0.16	0.16 ± 0.17	0.18 ± 0.27	116.7 ± 104.1[k]	220.0 ± 503.2[k]
TO6	8.88 ± 7.22	6.46 ± 7.44	14.6 ± 13.5	9.0 ± 9.4	54.2 ± 65.9[l]	114.4 ± 229.6[l]
TO3	0.51 ± 0.23	0.43 ± 0.31	0.93 ± 0.76	0.84 ± 0.81	67.4 ± 85.4[m]	203.3 ± 431.3[m]
TO6:3	17.5 ± 14.1	13.9 ± 14.1	14.6 ± 12.2	10.7 ± 9.9	11.4 ± 78.8[n]	−6.5 ± 37.2[n]

LA = linoleic acid; GLA = γ-linolenic acid; DGLA = dihomo-γ-linolenic acid; AA = arachidonic acid; DTA = docosatetraenoic acid; AL = α-linolenic acid; EPA = eicosapentaenoic acid; DPA = docosapentaenoic acid; DHA = docosahexaenoic acid; TO6 = total omega-6 fatty acid contant; TO3 = total omega-3 fatty acid contant; TO6:3 = ratio of TO6 to TO3

* Expressed as a percentage of the total amount of fatty acids in the sample; Values with the same superscript are significantly different

increase in AA (P = 0.0138) compared with the responders.

Post-trial changes in the skin fatty acid concentrations were not as marked as the plasma changes (Table V). With the exception of group mean decreases in DGLA and DTA among the responders, skin levels tended to increase after the dietary trial. In most instances, the post-diet skin fatty acid concentrations of the responders or nonresponders were not significantly different. Responders had significantly lower post-trial skin levels of DGLA (P = 0.0041), DTA (P = 0.037), and AL (P = 0.0000) compared with the nonresponders. Group mean percentage change in skin fatty acid concentration could not be computed for GLA among the nonresponders and for EPA among both groups because the change in too many dogs was 0, resulting in insufficient data points. The group mean percentage change between the responders and nonresponders was not significant for LA but was significant for all other fatty acids. Nonresponders had a significantly greater increase in DGLA (P = 0.0035), AA (P = 0.0004), DTA (P = 0.0012), AL (P = 0.0111), DPA (P = 0.0045), DHA (P = 0.0411), TO6 (P = 0.0017), and TO3 (P = 0.0002). Responders had a significantly greater increase in TO6:3 (P = 0.0203).

In the Pearson correlation testing, responders had excellent correlation of plasma LA to GLA (0.8706), plasma GLA to DGLA (0.8471), and plasma AA to DTA (0.8802). Nonresponders had excellent correlation of plasma GLA to DGLA (0.9548) and plasma AA to DTA (0.9897). No correlation of omega-6 fatty acid dietary change to plasma change was found in the responders or nonresponders. Correlation of dietary to plasma omega-3 fatty acids was very poor. The only excellent correlation found was for plasma EPA to DHA (0.9232). Matrices comparing plasma changes to skin changes for the omega-6 fatty acids of the nonresponders and the omega-3 fatty acids for both the responders and nonresponders could not be computed because too many cases were eliminated for zero values. Responders had excellent correlation between skin LA to GLA (0.9104) and skin DGLA to AA (0.9428). No correlation of omega-3 fatty acid plasma change to skin change could be detected.

DISCUSSION

The pruritus in 8 of 18 dogs (44.4%) in this study was decreased (good to excellent responses) when they consumed the test diet. The favorable response was observed after 7 to 21 d on the diet, and was lost 3 to 14 d after the diet was withdrawn. Control of pruritus was achieved again after the test diet was readministered, and it was maintained for over 1 to 2 y. These data indicate that the responses were not due to coincidental improvement. There was no relationship among sex, duration of disease, and the number of positive intradermal skin test results, and the response to the test diet. This has been previously reported in studies assessing the efficacy of various orally administered antipruritic agents in allergic dogs (18,19,23). In this study, older dogs did not respond as well to the test diet as did younger dogs. The reason for the poorer response of the older dogs is unknown.

Information on the fatty acid profiles of commercial foods is not readily available. Since our data indicated that dietary fatty acid levels could modulate pruritus in some dogs, it was appropriate to compare the mean levels found in standard or premium commercial foods (Table III). The fatty acid levels within and between these types of foods varied greatly but only differed significantly in some of the omega-3 fatty acids. The premium foods had higher levels of AL, DPA (data not shown), and TO3. However, when the levels for the responders or nonresponders that ate standard food were compared to the levels for the same response group that ate premium food, no difference was detected. This indicates that the gross characterization of a dog's regular diet as standard or premium is of no predictive value in estimating its response to the test diet.

Since dietary restriction to confirm or negate the diagnosis of food hypersensitivity was conducted for 4 to 6 wk in our dogs and the test diet's primary ingredients were lamb and rice, ingredients found commonly in hypoallergenic diets, it could be argued that some of the response seen in our atopic dogs was due to control of an unrecognized coincidental food

hypersensitivity. Certainly atopy and food hypersensitivity are known to coexist in some dogs (27–29). Some authors have reported that maximum improvement is not seen in some food hypersensitive dogs until they have consumed the hypoallergenic diet for 10 to 13 wk (28,30), and that 12.4% to 25.5% of food hypersensitive dogs will not show maximum improvement if the hypoallergenic diet is fed for only 4 to 6 wk (28,30). While we agree, in general, with these observations, we and others (31,32) believe that the key word here is "maximum." In our experience, any dog not showing any reduction of pruritus after 4 to 6 wk of strict dietary restriction has not improved with continued feeding of the hypoallergenic diet. None of the dogs in this study showed any lessening of their pruritus while eating the homecooked diet. In addition, all of our dogs had complete relief of their pruritus while receiving anti-inflammatory doses of prednisone, whereas only 0 to 58.3% of food hypersensitive dogs are reported to have a complete elimination of pruritus when so treated (28,30). We are confident that none of our dogs had concurrent food hypersensitivity.

We assume that the control of pruritus in the dogs reported herein was achieved by the omega-3/omega-6 fatty acid-content of the diet. These fatty acids are known to be useful in controlling pruritus in a certain percentage of atopic dogs (18–20), and the plasma concentrations of these fatty acids, for the most part, were increased while the dogs were consuming the test diet. Other investigators have reported similar, though often less consistent and less dramatic, changes in plasma fatty acid concentrations during the administration of various omega-3 and/or omega-6 fatty acid-containing products (33–39). Direct comparison with our data cannot be made due to differences in the products being administered (sources of fatty acids; doses of fatty acids; ratios of fatty acids; duration of administration of fatty acids; other ingredients in the product) and the laboratory methods employed.

There is a clear difference in the fatty acid data between the responders and nonresponders in this study (Tables IV and V). With the exception of LA in the responders, the switch to the test diet resulted in a 5% to 4495% increase in dietary levels of the various fatty acids. As expected, plasma levels, except for DTA, increased after the dogs ate the test diet for 8 wk. However, the pattern of plasma change is different from that expected. Nonresponders had a greater increase in their dietary fatty acid levels but tended to have lower plasma increases than the responders. A similar inconsistent response is seen when skin changes are compared to plasma changes. Although nonresponders had less of an increase in their plasma fatty acid levels, they had a greater percentage increase in their skin fatty acids for all fatty acids except LA.

When normal and atopic dogs were fed corn oil, the atopic dogs had significantly lower peak serum triglyceride levels, suggesting an abnormality in fat absorption or clearance (40). Other work suggests that atopic dogs have a Δ-6-desaturase deficiency and metabolize fats differently than non-atopic dogs (16,17). If our data are correct and are not influenced by the small sample size, it would appear that we have identified 2 subsets of atopic dogs. Our nonresponders had a greater dietary change in fatty acid levels than the responders, but had a smaller increase in their plasma fatty acid levels. This inconsistency can be explained by a greater abnormality in fat absorption, metabolism, or clearance in this group compared with the responders. Data from normal and a greater number of atopic dogs will be necessary to characterize our findings more completely.

The Pearson correlation data suggests that there also is a difference in fatty acid metabolism between our responders and nonresponders. Responders had excellent correlation of their plasma LA to GLA, GLA to DGLA, and AA to DTA levels. Nonresponders had excellent correlation of their plasma GLA to DGLA and AA to DTA levels. Conversion of LA to GLA is catalyzed by the enzyme Δ-6-desaturase and conversion of DGLA to AA is catalyzed by Δ-5-desaturase (41). If such conversions proceed in an expected biochemical manner, the amount of product of the conversion should correlate with the amount of substrate, provided that the enzyme is not saturated with excess substrate. Since there was no correlation of DGLA to AA in both the responders and nonresponders, it would appear that both groups have an abnormality in DGLA metabolism which can be explained by a Δ-5-desaturase deficiency. Nonresponders also had an abnormality in LA metabolism, suggesting a Δ-6-desaturase deficiency. The Δ-6-desaturase deficiency could also be present but less marked in the responders, as has been suggested (16,17). Data from normal dogs would be necessary to clarify this point. Further studies on the fatty acid metabolism of atopic dogs will be necessary to support or refute our observations.

The skin changes are very difficult to explain. Responders had significantly greater plasma increases of LA, DGLA, and AL than nonresponders, yet had the same level of skin change for LA and lower increases in DGLA and AL. Responders and nonresponders had similar plasma increases of DPA, DHA, TO6, and TO3, yet the nonresponders had significantly greater skin increases in these fatty acids. These inconsistencies may be a result of the technique used to collect and process skin samples, or they may reflect some metabolic difference between the groups. Since correlation matrices could not be computed because of too many missing data points, the authors cannot explain the skin changes.

Although omega-3 and omega-6 fatty acids are known to modulate eicosanoid (prostaglandin, leukotriene) synthesis (13,15,16,42–44), and eicosanoids are known to be involved in the inflammatory responses in canine skin (1,42,45,46), much remains to be learned about the use of these fatty acids in the therapy of canine allergic skin disease. Important issues to be resolved include optimum dose of the omega-3 and omega-6 fatty acids; the optimum ratio of these fatty acids; whether omega-3 fatty acids are preferable to omega-6 fatty acids or vice-versa, or are both needed; and the appropriate duration of therapy needed to determine maximum benefit to the patient (17).

The dosage recommendations for omega-3/omega-6 fatty acid-containing commercial products used in dogs are

largely empirical (19,33,43,44,47). The commercial product for which most of the published information is available (DVM Derm Caps, DVM Pharmaceuticals, Miami, Florida, USA) satisfactorily controls pruritus in 11.1% to 26.7% of atopic dogs when used according to manufacturer's recommendations (18–20). In one study (23), dogs that failed to respond to the manufacturer's recommended dosage also failed to respond to twice that dosage. Reports from England, wherein a similar commercial product (EfaVet, Efamol Vet, Guildford, UK) was used, indicated that many atopic dogs required up to 10 times the usual dosage of the product before satisfactory control of pruritus was attained (34–37). However, it is impossible to fully assess these reports as the data for individual dogs are not presented. Thus, one cannot determine how many dogs respond to the usual dosage of the product as opposed to 4, 6, or 10 times this dosage.

Our data supports the idea that some atopic dogs require much higher levels of fatty acids, especially of the omega-3 type, to control their pruritus than provided by commercial dietary supplements at the recommended dosage. Eleven of our dogs (Cases 1–8,11,16,18) had received prior treatment with a commercial product at the manufacturer's recommended dosage and had not responded. As administered, the supplement provided 29.6, 1.1, 1.6, and 1.1 mg/kg BW/day of LA, GLA, EPA, and DHA, respectively. Seven of these 11 dogs (64%) (Cases 1–4,6,8,11) had good or excellent responses to the test diet. Since the levels found in the supplement are approximately 3 to 10 times less than those found in the test diet, the obvious reason for the different response is inadequate supplementation. However, the supplement figures are misleading, since they do not account for the amount of omega-3/omega-6 fatty acids in the dogs' base diets. When the base dietary level for the 9 dogs where it was known (Table III) was added to the amount received in the supplement, the test diet provided less LA, about 4.5 times more GLA and EPA, and 7 times more DHA. To receive these levels, the dogs would have to have been given the supplement at approximately 6 times the manufacturer's suggested dosage. Supplementation at that level might be cost prohibitive for many owners. When the pre-trial dietary levels of the supplement failures that did or did not respond to the test diet are examined, the diets differed significantly in their AL, EPA, DHA, and TO3 content. Nonresponders had much higher levels of all these fatty acids. Since there were only 2 dogs in the nonresponder group, these data must be interpreted cautiously. If valid, they indicate that atopic dogs that are eating foods high in omega-3 fatty acids are unlikely to respond to omega-3/omega-6 fatty acid supplements or the test diet.

The proper ratio of omega-6: omega-3 fatty acids that would provide optimum anti-inflammatory/antipruritic activity has also been unclear. Early reports indicated that an appropriate ratio of omega-6: omega-3 fatty acids was 4:1 (43,44,47). However, these recommendations, apparently, were not based on any studies performed in dogs. Recently, trials were conducted in normal dogs wherein the effects of feeding various ratios of omega-6:omega-3 fatty acids on leukotriene synthesis in skin and peripheral neutrophils were studied (48). Experimental diets, containing omega-6:omega-3 fatty acid ratios of 5:1, 10:1, 25:1, 50:1, and 100:1 were fed for 12 wk. Only the diets containing ratios of 5:1 and 10:1 significantly decreased leukotriene B_4 (proinflammatory eicosanoid) synthesis and increased leukotriene B_5 (noninflammatory eicosanoid) synthesis in skin and isolated neutrophils. This study demonstrated that a diet with an overall dietary omega-6:omega-3 fatty acid ratio of 5.5:1 satisfactorily controlled pruritus in 8 of 18 atopic dogs, 11 of which had not shown any clinical benefit with a commercial fatty acid supplement. Accordingly, the overall dietary omega-6/omega-3 fatty acid ratio is probably an important modulator of the inflammatory response both in normal (48) and certain atopic dogs.

The TO6:3 can be carefully controlled in dog foods, such as the test diet, but would be difficult to influence with supplements, since basal dietary levels would be difficult to determine. Some investigators have reported excellent control of pruritus in many atopic dogs when large doses of gamma-linoleic enriched omega-6 fatty acids (34,36,37,49) or omega-3 fatty acids (13,49,50) were added to the dogs' basic diet. If the foods those dogs were eating were similar to our dogs' diets, the addition of any significant amount of omega-6 fatty acids would drive the omega-6:omega-3 ratio higher. Since commercial foods are high in omega-6 fatty acids, over 40 mg/kg BW/day of omega-3 fatty acids would have to be added before the desired ratio was approached. Until basal dietary fatty acid levels have been considered for dogs responding to fatty acid supplements, the reason for their response will remain obscure. As this study demonstrates, not all atopic dogs respond in an identical fashion. Accordingly, there may be no such thing as "the best" omega-3/omega-6 fatty acid-containing diet for all dogs. It may be important to try more than 1 type in some patients, similar to what is done with antihistamines (1,17,37,49).

It has been suggested, without data gathered from pruritic dogs, that omega-3/omega-6 fatty acid supplements must be continued for 3 to 8 wk before an assessment of its effectiveness can be made (16,43,44). Some authors have suggested 12 wk of therapy (16,17,38). This latter recommendation was based on the time required for fatty acid levels to peak in canine skin specimens and not on any effect on canine pruritus. On the other hand, clinical studies have repeatedly shown that pruritus is controlled in 11.1% to 26.7% of the dogs within 1 to 2 wk of therapy (18–20,23,49). In this study, the test diet was fed for 8 wk, but all the dogs that experienced relief from pruritus did so within 7 to 21 d.

Another concern expressed in the literature is the so-called "wash-out" period following withdrawal of fatty acid therapy (16,43,44,49). Because tissue levels of these fatty acids slowly decline over a 3-week period after oral administration is discontinued, it was assumed that this could also have clinical implications for skin disease. Again, when evaluating pruritus, numerous clinical trials (18–20,23,49) and this study have

shown that the antipruritic activities of fatty acid supplements are lost within 2 to 14 d.

Five dogs in our study had immediate positive intradermal skin test reactions to flea antigen in addition to their other reactions. None of these dogs responded to the test diet. Although the sample size is too small to allow meaningful conclusions, coexisting flea bite hypersensitivity could be an important prognostic factor in atopic dogs treated with omega-3/omega-6 fatty acid products. This would not be surprising given the complex immunopathogenesis of flea bite hypersensitivity, which includes type I and type IV hypersensitivity reactions, cutaneous basophil hypersensitivity, and, perhaps, the late-phase immunoglobulin E reactions (51). As anywhere from 36% to 80% of atopic dogs are concurrently flea hypersensitive (51,52), this could be an important consideration.

In conclusion, under the conditions of our study, a commercial lamb and rice diet was found to control pruritus in 44.4% of 18 atopic dogs. It is suggested that the antipruritic effect of this diet is due to its fatty acid profile, especially the omega-3 component and the omega-6:omega-3 ratio. Our data suggests that there may be subsets of atopic dogs whose fatty acid metabolism is so different from normal or other atopic dogs that controlled fatty acid intake will have little or no effect on their atopic pruritus.

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