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The Clinical Efficacy of Dietary Fat Restriction in Treatment of Dogs with Intestinal Lymphangiectasia

H. Okanishi, R. Yoshioka, Y. Kagawa, and T. Watari

Background: Intestinal lymphangiectasia (IL), a type of protein-losing enteropathy (PLE), is a dilatation of lymphatic vessels within the gastrointestinal tract. Dietary fat restriction previously has been proposed as an effective treatment for dogs with PLE, but limited objective clinical data are available on the efficacy of this treatment.

Hypothesis/Objectives: To investigate the clinical efficacy of dietary fat restriction in dogs with IL that were unresponsive to prednisolone treatment or showed relapse of clinical signs and hypoalbuminemia when the prednisolone dosage was decreased.

Animals: Twenty-four dogs with IL.

Methods: Retrospective study. Body weight, clinical activity score, and hematologic and biochemical variables were compared before and 1 and 2 months after treatment. Furthermore, the data were compared between the group fed only an ultra low-fat (ULF) diet and the group fed ULF and a low-fat (LF) diet.

Results: Nineteen of 24 (79%) dogs responded satisfactorily to dietary fat restriction, and the prednisolone dosage could be decreased. Clinical activity score was significantly decreased after dietary treatment compared with before treatment. In addition, albumin (ALB), total protein (TP), and blood urea nitrogen (BUN) concentration were significantly increased after dietary fat restriction. At 2 months posttreatment, the ALB concentrations in the ULF group were significantly higher than that of the ULF + LF group.

Conclusions and Clinical Importance: Dietary fat restriction appears to be an effective treatment in dogs with IL that are unresponsive to prednisolone treatment or that have recurrent clinical signs and hypoalbuminemia when the dosage of prednisolone is decreased.

Key words: Canine; Inflammatory bowel disease; Protein-losing enteropathy.

Protein-losing enteropathy (PLE) refers to intestinal disorders characterized by gastrointestinal protein loss of such magnitude as to result in hypoalbuminemia.[1,2] Intestinal lymphangiectasia (IL), a type of PLE, involves dilatation of lymphatic vessels within the gastrointestinal tract.[3] IL may be a primary disease, but typically is a secondary process in dogs.[4,5] The most common mechanisms associated with secondary IL in dogs include increased lymphatic pressure caused by inflammatory bowel disease (IBD), lymphoma, or infectious diseases, and increased venous pressure at the level of the thoracic duct attributable to right-sided heart failure, pericarditis, or pericardial effusion.[6] Clinical signs include vomiting, diarrhea, weight loss, and ascites, but these signs may not always be present. Laboratory abnormalities associated with IL include hypoalbuminemia, panhypoproteinemia, lymphopenia, hypocalcemia, and hypocholesterolemia.[7] Definitive diagnosis of IL is obtained by histopathologic evaluation of intestinal biopsy specimens, which can be obtained surgically or endoscopically.[6,7]

There are several treatment modalities for PLE, including immunosuppressive agents (eg, prednisolone, cyclosporine), dietary treatment (low-fat or hypoallergenic diet), hydroxeythyl starches, and nutritional supplementations (vitamins or minerals). Prednisolone treatment is commonly used for IL (particularly with IBD)[7,8] and is effective in many cases. However, some

Abbreviations:

ACVP	American College of Veterinary Pathologists
ALB	albumin
BUN	blood urea nitrogen
Ca	calcium
CBC	complete blood count
CCECAI	canine chronic enteropathy clinical activity index
CRP	c-reactive protein
DER	daily energy requirement
IBD	inflammatory bowel disease
IL	intestinal lymphangiectasia
LF	low-fat
LPE	lymphocytic-plasmacytic enteritis
PCV	packed cell volume
PLE	protein-losing enteropathy
T. Chol	total cholesterol
TP	total protein
ULF	ultra low-fat
WBC	white blood cell
WSAVA	World Small Animal Veterinary Association

From the Laboratory of Comprehensive Veterinary Clinical Studies, Department of Veterinary Medicine, College of Bioresource Sciences, Nihon University, Kanagawa, Japan (Okanishi, Yoshioka, Watari); and the NORTH LAB Inc, Hokkaido, Japan (Kagawa).

Corresponding author: Toshihiro Watari, Laboratory of Comprehensive Veterinary Clinical Studies, Department of Veterinary Medicine, Faculty of Bioresource Sciences, Nihon University, 1866 Kameino, Fujisawa, Kanagawa 252-0880, Japan; e-mail: watari@brs.nihon-u.ac.jp.

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dogs with IL caused by IBD have an unsatisfactory response to prednisolone treatment or recurrence of clinical signs or hypoalbuminemia when the prednisolone dosage is decreased.[8,9] Steroid treatment may be ineffective because of severe mucosal inflammation or malabsorption, and clinical signs may recur when the prednisolone dosage is decreased because of exacerbation of mucosal inflammation.

An ultra low-fat (ULF) diet composed of turkey breast and potato previously was proposed as part of the treatment for PLE in dogs by Peterson and Willard.[10] ULF diets are thought to decrease the leakage of protein and lipid into the intestinal lumen more than low-fat (LF) diets because of decreased lymphatic pressure. However, objective information on the efficacy of dietary fat restriction including ULF dietary treatment in PLE dogs has not been reported, and limited clinical data on the efficacy of dietary fat restriction in canine PLE are available.

Therefore, the purpose of this present study was to evaluate the clinical efficacy of dietary fat restriction in dogs with IL that were unresponsive to prednisolone treatment or experienced a recurrence of clinical signs or hypoalbuminemia when the prednisolone dosage was decreased. Furthermore, we investigated the possibility of a reduction in prednisolone dosage with dietary fat restriction.

Materials and Methods

Dogs

Medical records of 27 dogs with IL fed ULF or ULF + LF diet, among dogs admitted to the Animal Medical Center of Nihon University from November 2010 to March 2013 with signs of chronic gastrointestinal disease (ie, vomiting, diarrhea, weight loss) of more than 3 weeks' duration, were reviewed for inclusion in the study. The dogs underwent a thorough investigation, including complete blood count, serum biochemistry profile, parasitologic and bacteriologic examination of feces (for nematodes, *Giardia* spp., *Trichomonas* spp., and *Campylobacter* spp.), urinalysis, radiographic examination, ultrasound examination, and endoscopy with intestinal biopsy sampling to exclude other causes of gastrointestinal signs. Inclusion criteria included hypoalbuminemia (ALB <2.7 g/dL) and histopathologic confirmation of IL. Three of 27 cases were excluded because they exhibited hepatic dysfunction (increased bile acid concentrations), renal disease (increased blood urea and serum creatinine concentrations and proteinuria), or blood loss (decreased packed cell volume and gastrointestinal bleeding). One case showed changes consistent with hepatic dysfunction on the serum biochemical profile (decreased blood urea and glucose concentrations, and increased total bilirubin concentration), but was included because the bile acid stimulation test result was normal. Proteinuria was excluded in 24 dogs on the basis of a negative urine dipstick test or a urine protein:creatinine ratio <0.5.

All dogs received antibacterial (metronidazole,[a] 10 mg/kg, PO, q12h, >2 weeks) and dietary treatment consisting of an antigen-restricted diet or a hydrolyzed diet for at least 2 weeks. Furthermore, all dogs received dietary treatment consisting of LF dry canine food (Veterinary Diet Gastrointestinal Low Fat,[b] n = 10; Prescription Diet i/d Canine, n = 3; Prescription Diet w/d Canine,[c] n = 11; >3 weeks). The diet and antibiotic trials were performed concurrently. The dogs did not show improvement in ALB concentration or clinical signs after these treatments and intestinal biopsy was performed. Prednisolone treatment was instituted after IL had been definitively diagnosed. The initial prednisolone dosage was 1–2 mg/kg/day PO (1 mg/kg/day, n = 13; 2 mg/kg/day, n = 11), according to commonly used dosages,[7,8] and the dosage was decreased every 2–4 weeks if a satisfactory response, based on improvement of clinical signs and ALB concentration, was achieved.

The criteria for commencement of dietary fat restriction were as follows: (1) improvement of ALB concentration and clinical signs with prednisolone treatment but decrease in ALB concentration and exacerbation of clinical signs with reduction in prednisolone dosage or (2) no improvement of ALB concentration and clinical signs after prednisolone treatment for >4 weeks. The medical records of dogs that received dietary fat restriction were retrospectively reviewed.

The ULF diet was based on the report by Peterson and Willard and was composed of 1 part chicken breast without skin plus 2 parts white potato without skin (all boiled, baked, or microwaved) or rice.[10] We replaced the turkey breast in the ULF diet of Peterson and Willard with chicken breast in this present study. Chicken breast is composed mainly of protein with hardly any fat, and provides 125 kcal per 100 g meat (including protein, 27.3 g; fat, 1.0 g; carbohydrate, 0 g; ash, 1.1 g; water, 70.6 g; sodium, 29 mg; potassium, 350 mg; calcium, 4 mg; magnesium, 32 mg; phosphorus, 220 mg; iron, 0.3 mg; zinc, 0.7 mg; copper, 0.03 mg; manganese, 0.01 mg; vitamin B_1, 0.09 mg; and vitamin B_2, 0.12 mg). White potato is composed mainly of carbohydrates with little protein, and provides 84 kcal per 100 g potato (including protein, 1.5 g; fat, 0.1 g; carbohydrate, 19.7 g; ash, 0.6 g; water, 78.1 g; sodium, 1.0 mg; potassium, 330 mg; calcium, 2 mg; magnesium, 20 mg; phosphorus, 23 mg; iron, 0.3 mg; zinc, 0.2 mg; copper, 0.08 mg; manganese, 0.13 mg; vitamin C, 15 mg; and vitamin B_6, 0.16 mg).[11] Among the 24 dogs that received dietary fat restriction, dogs fed only the ULF diet were categorized as the ULF group, and dogs fed 1 part ULF diet plus 1 part LF dry canine food (Veterinary Diet Gastrointestinal Low Fat, Royal Canin[b] or Prescription Diet w/d Canine[c]) were categorized as the ULF + LF group. The ULF and LF combination diet was used because the ULF diet alone may lead to nutritional imbalances of minerals and vitamins. Therefore, LF dry canine food (complete and balanced dry canine food) was mixed with the ULF diet in equal parts. We considered that the blend would be more nutritious than the ULF diet alone, and have a lower fat content than the LF diet alone. However, certain dogs were fed only the ULF diet because we considered that the ULF diet alone might decrease the leakage of protein and lipid into the intestinal lumen more effectively than the ULF + LF diet because of decreased lymphatic pressure. Therefore, we used both the ULF and ULF + LF diets in the study cases, and compared the efficacy between these groups in this retrospective study. The total calorie intake of all dogs was based on daily energy requirement (DER). DER was calculated as resting energy requirement for ideal weight × 1.0 (used for poorly nourished dogs).

Data Collection

Body weight was recorded before and after the treatment. Each dog was given a clinical score by the canine chronic enteropathy clinical activity index (CCECAI) scoring system,[12] and the scores were recorded before and after treatment. The scoring criteria included attitude, activity, appetite, vomiting, feces consistency, feces frequency, weight loss, ALB concentration, ascites and peripheral edema, and pruritus. By the CCECAI, the abovementioned 9 prominent gastrointestinal signs were scored from 0 to 3 according to the magnitude of change. The CCECAI

assessment was performed by a clinician with informed consent from the client at the time of the clinical examination.

The following biochemical variables were compared before and after the treatment: ALB, total protein (TP), total cholesterol (T. Chol), blood urea nitrogen (BUN), calcium (Ca), and C-reactive protein (CRP). In addition, hematologic variables including packed cell volume (PCV) and white blood cell (WBC) count were analyzed before and after treatment.

Mucosal biopsy specimens were obtained from the duodenum by a single endoscopist. Under general anesthesia, tissue sampling was performed by endoscopy[d] according to the World Small Animal Veterinary Association (WSAVA) guidelines.[13] Multiple mucosal biopsies of the descending duodenum were obtained from each dog with biopsy forceps,[e] and the samples were used for histopathologic analysis. Samples were immediately placed in 10% formalin, and hematoxylin and eosin-stained sections were prepared. Histopathologic examination of the sections was carried out by an American College of Veterinary Pathologists board-certified pathologist, and each case was scored according to histopathologic standards established in the WSAVA guidelines. In this standard assessment of duodenal mucosa, 5 morphologic features (ie, villous stunting, epithelial injury, crypt distension, lacteal dilatation, and mucosal fibrosis) and 4 types of infiltrating leukocytes (intraepithelial lymphocytes, lamina propria lymphocytes and plasma cells, lamina propria eosinophils, and lamina propria neutrophils) were scored from 0 to 3 according to guidelines (0, normal; 1, mild; 2, moderate; 3, marked), from which a final diagnosis was determined. Body weight, clinical score, and laboratory findings were analyzed in all dogs on the day of definitive diagnosis (day 0), just before commencing dietary fat restriction (pretreatment), and after the onset of dietary fat restriction (1 and 2 months posttreatment). Furthermore, these data were compared at 1 and 2 months posttreatment between the ULF and ULF + LF groups.

Statistical Analyses

Data that were not normally distributed were reported as medians (ranges). The results were assessed for normality by the Kolmogorov–Smirnoff test. The data were not normally distributed. The Friedman test and Wilcoxon signed-rank test were used to compare body weight, CCECAI, laboratory findings, and histopathologic score at day 0 (day of definitive diagnosis), pretreatment (just before commencing dietary fat restriction), and 1 and 2 months posttreatment in PLE dogs. The Wilcoxon signed-rank test was performed to compare measurements taken at day 0 and pretreatment, as well as to compare the measurements taken pretreatment and after 1 or 2 months of treatment. The Wilcoxon rank-sum test was used to compare the CCECAI and laboratory findings between the ULF and ULF + LF groups. Twelve dogs were included in the ULF group and 12 (Royal Canin GI Low Fat, n = 5; Hill's w/d, n = 7) in the ULF + LF group. A Mann–Whitney test was used to compare the measurements taken between groups at 1 and 2 months posttreatment. Statistical significance was set at $P < .05$. All statistical analyses were performed by a commercially available statistical software system.[f]

Results

Criteria

Twenty-four cases met the inclusion criteria. There were 3 castrated male, 10 spayed female, 8 intact male, and 3 intact female dogs. The median age was 8.5 years (range, 4–13 years) for all dogs. The dog breeds in this present study included Papillon (3), Yorkshire Terrier (3), Maltese (2), Miniature Dachshund (2), French Bulldog (2), Shetland Sheepdog (2), Shiba Inu (1), Toy Poodle (1), Pomeranian (1), Boston Terrier (1), Miniature Pinscher (1), Shih Tzu (1), American Cocker Spaniel (1), Border Collie (1), Italian Greyhound (1), and Airedale Terrier (1).

On endoscopic examination, mucosal hyperemia was observed in 9/24 dogs (37.5%), mucosal edema in 10/24 dogs (41.6%), pinpoint white foci in 15/24 dogs (62.5%), mucosal roughness in 14/24 dogs (58.3%), and erosions in 1/24 dog (4%).

All study dogs were diagnosed histopathologically as having IL. The median histopathologic score was 3 (range, 1–13) in IL dogs. The severity of lesions and the type of inflammation in the cases are shown in Table 1. The histopathologic grades of villous stunting ranged from score 0 (normal) to score 2 (moderate) in IL dogs. There also were few observations of villous epithelial injury in IL dogs (n = 4/24), and the grade in 1 case was score 1 (mild) and in 3 cases was score 2. In addition, there were also few observations of crypt distention in IL dogs (n = 5/24), and the grade in 1 case was score 1 and in 4 cases was score 3 (marked). Several grades of lacteal dilatation were seen from score 1 to score 3, and the grade in 16 cases was score

Table 1. Results of histopathologic findings in duodenal mucosa of IL dogs.

Histopathologic Score Morphologic Features	IL Dogs (n = 24)	Inflammation	IL Dogs (n = 24)
Villous stunting	14	Intraepithelial lymphocytes	2
Score 0	10	Score 0	22
Score 1	11	Score 1	2
Score 2	2	Score 2	0
Score 3	1	Score 3	0
Epithelial injury	4	Lamina propria lymphocytes and plasma cells	18
Score 0	20	Score 0	6
Score 1	1	Score 1	12
Score 2	3	Score 2	5
Score 3	0	Score 3	1
Crypt distention	5	Lamina propria eosinophils	1
Score 0	19	Score 0	23
Score 1	1	Score 1	1
Score 2	0	Score 2	0
Score 3	4	Score 3	0
Lacteal dilatation	24	Lamina propria neutrophils	2
Score 0	0	Score 0	22
Score 1	16	Score 1	2
Score 2	6	Score 2	0
Score 3	2	Score 3	0
Mucosal fibrosis	0		

Score 0 = normal; Score 1 = mild; Score 2 = moderate; Score 3 = marked. IL, intestinal lymphangiectasia.

1, in 6 cases was score 2, and in 2 cases was score 3. However, no observations of mucosal fibrosis were made in IL dogs. Increased numbers of epithelial lymphocytes were considered mild in 2 dogs, and infiltration of lymphocytes and plasma cells was considered mild to marked in the lamina propria of 18 dogs. Lamina propria eosinophils were observed in 1 dog, and neutrophils in 2 dogs.

Ten of 24 cases were not responsive to steroid treatment, and had received prednisolone treatment for >4 weeks before dietary fat restriction was added to the treatment. The dosages of prednisolone just before dietary fat restriction was instituted were 2 mg/kg/day (n = 2) and 1 mg/kg/day (n = 8). All dogs continued prednisolone while being treated with dietary fat restriction, and metronidazole was continued as the other medication during treatment with dietary fat restriction. Fourteen of 24 dogs were responsive, but experienced a decrease in serum ALB concentration and exacerbation of clinical signs with reduction in prednisolone dosage. These dogs were given prednisolone treatment for >4 weeks before dietary fat restriction was added to the treatment. The dosages of prednisolone just before dietary fat restriction was started were 1.5 mg/kg/day (n = 2), 1 mg/kg/day (n = 4), 0.75 mg/kg/day (n = 1), and 0.5 mg/kg/day (n = 7).

Nineteen of 24 (79%) dogs responded satisfactorily to the dietary fat restriction, and the prednisolone could be stopped or the dosage decreased relative to that before dietary fat restriction at 2 months posttreatment. The final dosage of prednisolone was 0 mg/kg/day in 5/19 dogs, 0.25 mg/kg, q48h in 5/19 dogs, 0.25 mg/kg/day in 6/19 dogs, and 0.5 mg/kg/day in 3/19 dogs. The remaining 5 dogs (ULF, n = 3; ULF + LF, n = 2) required increased prednisolone dosage because of unresponsiveness to dietary fat restriction. Two of the dogs (ULF group) were reluctant to eat the diet. The prednisolone dosage was increased and cyclosporine was added, but the dogs died without any improvement in laboratory findings or clinical signs. In another dog (a Shiba Inu), increased ALB and TP concentrations were observed, but there was no improvement in clinical signs. Thereafter, the prednisolone dosage was increased and cyclosporine was added, but the dog died with no response to this treatment. The remaining 2 dogs experienced increases in serum ALB and TP concentrations but no improvement in clinical signs. Clinical signs improved in these 2 dogs after the dosage of prednisolone was increased. These 5 dogs were included in the analysis at 1 month posttreatment, but excluded from the analysis at 2 months posttreatment because the dosages were increased during the period from 1 to 2 months posttreatment.

Analyses of CCECAI and Body Weight before and after Treatment

The cases were analyzed to assess body weight and CCECAI at day 0, pretreatment, and 1 and 2 months posttreatment. Of all 24 dogs at pretreatment, 8 had severe disease according to CCECAI score (>9), 7 had moderate disease according to CCECAI score (6–9), and 9 had mild disease according to CCECAI score (<6). Nonresponders to dietary fat restriction had moderate (3 dogs) or severe (2 dogs) disease according to CCECAI score, and none had mild disease.

Twenty-two of 24 cases showed decreased CCECAI after treatment. Furthermore, CCECAI was significantly decreased at 1 and 2 months posttreatment compared with pretreatment ($P < .001$ and $P < .001$, respectively) (Fig 1). However, there were no significant differences in body weight between pretreatment and 1 or 2 months posttreatment.

Analysis of Laboratory Findings before and after Treatment

The cases were analyzed regarding ALB, TP, T. Chol, BUN, Ca, CRP, PCV, and WBC at day 0, pretreatment, and 1 and 2 months posttreatment (Table 2). Twenty of 24 dogs experienced increased serum ALB concentrations after the treatment, and 14 of 24 dogs achieved normal serum ALB concentrations after treatment. ALB, TP, and BUN concentrations were significantly increased at 1 month and 2 months posttreatment compared with pretreatment (ALB: $P < .01$, $P < .001$; TP: $P < .01$, $P < .01$; BUN: $P < .05$, $P < .05$, respectively; Fig 1). The increase in the concentration of ALB from pretreatment to 1 month posttreatment was 26.3%, and from 1 month posttreatment to 2 months posttreatment was 12.5%. The increase in the concentration of TP from pretreatment to 1 month posttreatment was 18.6%, and from 1 month posttreatment to 2 months posttreatment was 3.9%. The increase in the concentration of BUN from pretreatment to 1 month posttreatment was 58.3%, and from 1 month posttreatment to 2 months posttreatment was 7.8%. There were no significant differences in PCV, T. Chol, and Ca between pretreatment and 1 or 2 months posttreatment (Fig 1). Furthermore, the CRP concentration did not differ significantly between pretreatment and 1 or 2 months posttreatment. The WBC count was significantly decreased at 2 months after treatment compared with pretreatment ($P < .01$), but there was no significant difference between pretreatment and 1 month posttreatment (Fig 1).

Comparison between the ULF and ULF + LF Groups after Treatment

There were no significant differences in the ALB concentration at day 0 (ULF group: median 2 g/dL, range 1.3–2.6; ULF + LF group: median 2 g/dL, range 0.5–2.6, $P = .52$) and pretreatment (ULF group: median 2.1 g/dL, range 1–2.2; ULF + LF group: median 1.8 g/dL, range 1–2.5, $P = .91$) between the ULF and ULF + LF groups (Table 3). At 2 months posttreatment, the ALB concentration in the ULF group was significantly higher than that in the ULF + LF group (ULF group: median 3 g/dL, range 2.1–3.3; ULF + LF group: median 2.4 g/dL, range 1.4–2.9, $P = .01$), although there was no significant difference

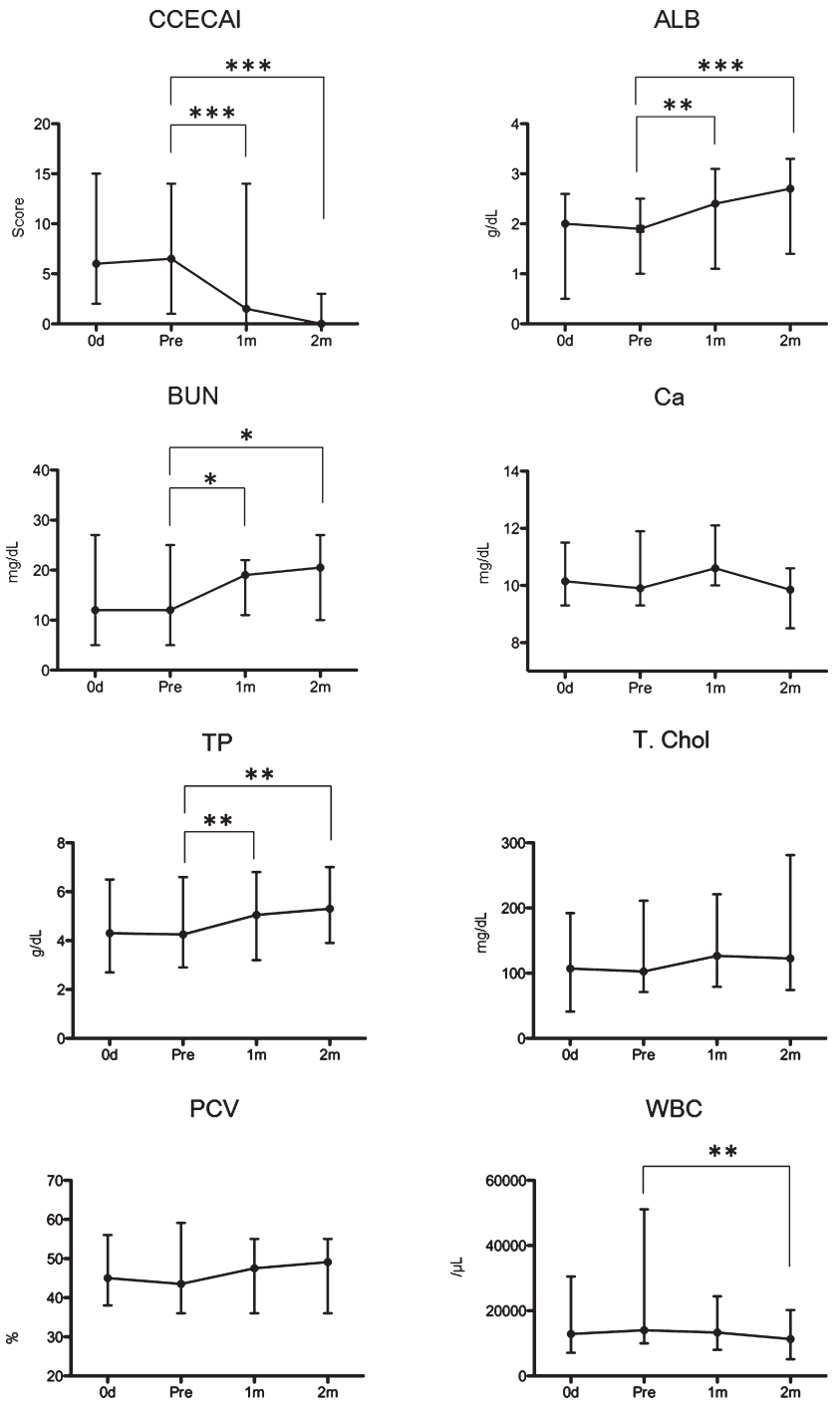

Fig 1. The changes of clinical score and laboratory findings from pretreatment to posttreatment in IL dogs with dietary fat restriction. Data are shown as the median with range for each finding. Significant differences between pretreatment and posttreatment (1 and 2 months posttreatment) are indicated as $*P < .05$; $**P < .01$; and $***P < .001$. 0d, day of the definitive diagnosis; Pre, just before starting dietary fat restriction; 1m, 1 month after dietary fat restriction; 2m, 2 months after dietary fat restriction.

between the ULF and ULF + LF groups at 1 month posttreatment (ULF group: median 2.6 g/dL, range 1.1–2.9; ULF + LF group: median 2.3 g/dL, range 1.7–3.1, $P = .15$, Fig 2). There was no statistically significant difference in the TP concentration between groups (Fig 2). Furthermore, there were no significant differences in CCECAI and the other laboratory findings at 1 and 2 months posttreatment between the ULF and ULF + LF groups.

Discussion

This present study evaluated the efficacy of dietary fat restriction in IL dogs. Nineteen of 24 dogs

Table 2. Results of clinical score, body weight, and laboratory findings before and after dietary fat restriction.

	Day 0			Pretreatment			1 Month Posttreatment				2 Months Posttreatment				
	Median	Range	n	Median	Range	n	Median	Range	n	*P*	Median	Range	n	*P*	Reference Range
CCECAI (score)	6	2–15	24	6.5	1–14	24	1.5	0–14	24	<.001	0	0–3	19	<.001	0–3
BW (kg)	5.3	1.6–18.6	24	4.2	1.5–19.5	24	4.2	1.9–21.1	24	.51	4.6	1.7–19.3	19	.71	–
ALB (g/dL)	2	0.5–2.6	24	1.9	1–2.5	24	2.4	1.1–3.1	24	<.01	2.7	1.4–3.3	19	<.001	2.7–3.8
TP (g/dL)	4.3	2.7–6.5	24	4.3	2.9–6.6	24	5.1	3.2–6.8	24	<.01	5.3	3.9–7.0	19	<.01	5.2–8.2
T. Chol (mg/dL)	107	41–192	18	102.5	71–211	18	126.5	79–221	18	.08	122.5	74–281	18	.16	110–320
BUN (mg/dL)	12	5–27	12	12	5–25	12	19	11–22	12	<.05	20.5	10–27	12	<.05	7–27
Ca (mg/dL)	10.1	9.3–11.5	6	9.9	9.3–11.9	6	10.6	10–12.1	6	.05	9.9	8.5–10.6	6	.34	7.9–12
CRP (mg/dL)	0	0–2.8	18	0	0–2.1	18	0	0–0.8	18	.20	0	0–0.6	18	.23	0–0.99
PCV (%)	45	38–56	15	43.5	36–59.1	15	47.5	36–55	15	.33	48.4	36–55	15	.24	37–55
WBC (/μL)	12,850	7,100–30,500	15	14,000	10,000–51,100	15	13,300	8,000–24,400	15	.11	11,300	5,100–20,200	15	<.05	6,000–17,000

CCECAI, canine chronic enteropathy clinical activity index; BW, body weight; ALB, albumin; TP, total protein, T. Chol, total cholesterol; BUN, blood urea nitrogen; Ca, calcium; CRP, C-reactive protein; PCV, packed cell volume; WBC, white blood cell.

Table 3. Results of ALB and TP concentration in ULF and ULF + LF group before and after dietary fat restriction.

	Day 0				Pretreatment				1 Month Posttreatment				2 Months Posttreatment				
	Median	Range	n	*P*	Median	Range	n	*P*	Median	Range	n	*P*	Median	Range	n	*P*	Reference Range
ALB (g/dL)																	
ULF	2.0	1.3–2.6	12	.52	2.1	1–2.2	12	.91	2.6	1.1–2.9	12	.15	3.0	2.1–3.3	9	.01	2.7–3.8
ULF + LF	2.0	0.5–2.6	12		1.8	1–2.5	12		2.3	1.7–3.1	12		2.4	1.4–2.9	10		
TP (g/dL)																	
ULF	4.6	2.7–6.5	12	.36	4.2	2.9–6.6	12	.75	5.2	3.2–6.8	12	.41	5.7	4.4–7.0	9	.07	5.2–8.2
ULF + LF	4.2	2.9–7.0	12		4.2	2.9–5.3	12		5.0	3.8–6.1	12		5.0	3.9–5.8	10		

ALB, albumin; TP, total protein; ULF, ultra low-fat; LF, low-fat.

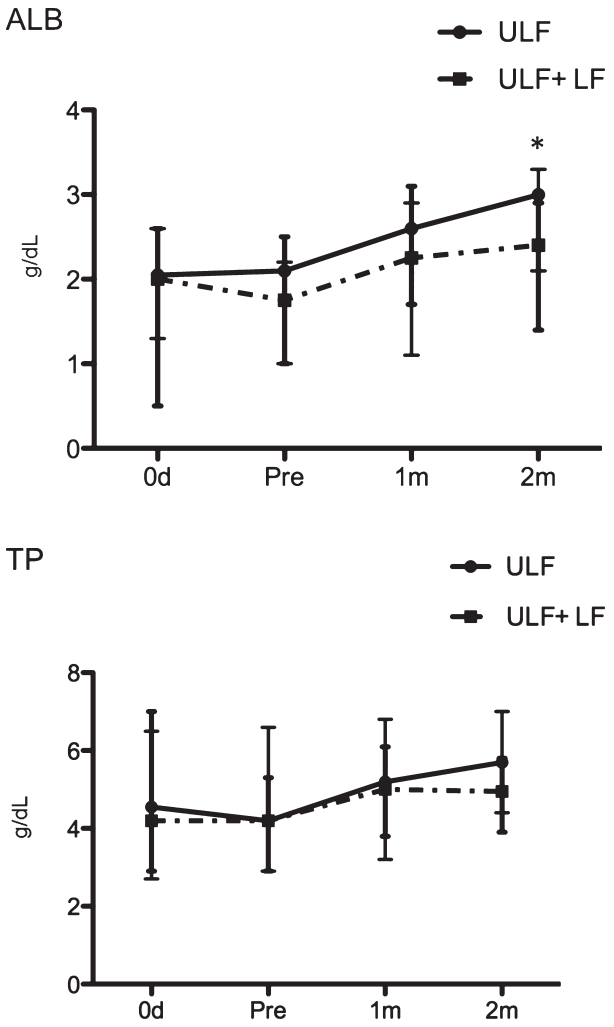

Fig 2. The changes in ALB and TP concentrations from day 0 to 2 months posttreatment in the ULF and ULF + LF groups. Data are shown as the median with range for each finding. Significant differences between groups are indicated as $*P < .05$. 0d, day of the definitive diagnosis; Pre, just before starting dietary fat restriction; 1m, 1 month after dietary fat restriction; 2m, 2 months after dietary fat restriction.

responded well to ULF or ULF + LF dietary treatment as 1 part of the treatment for PLE, and improvements in clinical signs and ALB concentration were observed in these dogs. Furthermore, the prednisolone dosage could be decreased in these dogs. However, dietary treatment was only 1 component of treatment for these dogs because they were receiving other treatments in addition to dietary treatment. Additional studies would be needed to investigate the efficacy of dietary fat restriction alone.

The median histologic score of 3 was low, and most cases had mild lacteal dilatation. We analyzed the histologic score only in the duodenal mucosa. Ileal biopsy specimens often are of higher quality than duodenal biopsy specimens in the diagnosis of IL.[7] Therefore, higher histologic grade and severe lacteal dilatation might have been found in the ileum of these dogs.

Prednisolone has catabolic effects that can be detrimental in dogs in negative energy balance.[14] Furthermore, prednisolone may exacerbate a preexisting hypercoagulable state and cause signs such as muscle weakness and lethargy.[15] Therefore, long-term use of prednisolone is problematic. In this present study, prednisolone could be administered at a dosage associated with minimal adverse effects (0.25 mg/kg/every other day) or discontinued in many of the cases (10/19 dogs). Thus, dietary fat restriction successfully enabled reduction in the dosage of prednisolone in the treatment of IL. However, 5 dogs were unresponsive to treatment and required increased dosages of prednisolone. The reasons for this lack of response might have been related to the fact that 2 dogs disliked the ULF diet and ate very little of it, and the Shiba Inu is a breed generally associated with a poor prognosis with LPE.[16,17] However, possible reasons remained unknown in the other 2 dogs. Dietary fat restriction may be effective in IL treatment, but this treatment modality requires further investigation to address the unresponsive PLE dogs. In addition, we investigated the efficacy of dietary fat restriction for up to 2 months of treatment. More extended studies are necessary to evaluate the therapeutic efficacy in IL dogs.

Intestinal lymphangiectasia causes the leakage of protein, lipid, and lymphocyte-rich lymph into the lumen, and induces secondary intestinal inflammation and edema.[5,18] Consequently, the intestinal inflammation contributes to clinical signs such as diarrhea, vomiting, and weight loss. In this present study, the CCECAI score was significantly lower after dietary fat restriction compared with scores at day 0 and pretreatment. The reason might be that lymphatic pressure was decreased by the dietary fat restriction, which may have contributed to improvement of clinical signs. Furthermore, the improved score in the PLE dogs might have been related to the relatively high palatability of chicken breast and white potato or rice. Nonresponders (5 dogs) had moderate or severe CCECAI scores, and none had mild scores. This result may indicate that dietary fat restriction has limited efficacy in patients with severe clinical signs.

The ALB, TP, and BUN concentrations were significantly increased at 1 month and 2 months posttreatment compared with pretreatment. The reason for these findings might be that the leakage of protein and lipid was decreased by the dietary fat restriction. In addition, the rates of increase in the concentrations of ALB, TP, and BUN were higher from pretreatment to 1 month posttreatment than from 1 month posttreatment to 2 months posttreatment. Willard previously reported that dogs with IL often show a marked increase in serum ALB concentration within 7–14 days of starting an ULF diet.[19] Therefore, dietary fat restriction may become effective in a relatively short period of time.

In this present study, there was only 1 case of hypocalcemia pretreatment, and most cases had normal Ca concentrations. In addition, there were no differences in

Ca concentration between pre- and posttreatment. These findings might have been because of maintenance of blood Ca concentration caused by secondary nutritional hyperparathyroidism. Secondary nutritional hyperparathyroidism results in release of Ca into the blood by bone decalcification. Consequently, blood Ca concentration is maintained.[20] The Ca concentration in the ULF diet used in this present study was inadequate for long-term management. In addition, we previously observed a PLE dog that had a pathologic fracture because of thinning of the cortical bone despite a normal blood Ca concentration. Therefore, supplementation of Ca and vitamin D may be important in IL dogs in the early stages of dietary fat restriction.

The WBC count was significantly decreased at 2 months posttreatment compared with pretreatment. Leukocytes generally increase in inflammation and infection. In addition, administration of prednisolone induces leukocytosis in the blood.[21] In this present study, the WBC count might have decreased because of a gradual decrease in the dosage of prednisolone or alleviation of enteritis by dietary fat restriction.

ALB concentration was significantly higher in the ULF than ULF + LF group at 2 months posttreatment. The reason for these findings might have been that the ULF-only diet was more limited in fat than the blend of ULF and LF food. In this present study, we used chicken breast without skin instead of turkey, because turkey is not commonly available in Japan. However, turkey without skin is lower in fat than chicken breast without skin,[11] and thus turkey is expected to yield the same (or better) clinical efficacy in IL dogs. In this present study, the ULF diet was composed of chicken breast without skin and rice or white potato without skin. This diet is very appropriate for restriction of fat, but it is inadequate for long-term nutritional management because of vitamin and mineral deficiencies.[22] The reason that a nutritionally inadequate diet was used in this present study was that the ULF diet had been reported to be effective and highly palatable, and useful as the first choice by Peterson and Willard.[10] However, they recommended a completely balanced ULF diet for long-term nutritional management.[10] Because IL dogs may experience chronic leakage of nutrients, nutritive supplementation (vitamins and minerals) may be needed at the start of treatment with dietary fat restriction. Additional studies are needed to clarify optimal ULF diets.

There were some limitations in this present study. One limitation was that the study sample was relatively small. The combined data of the ULF group and ULF + LF group were included in this present study because the number of cases fed only the ULF diet was small and prevented meaningful analysis. Larger number of samples may be needed to investigate the efficacy of dietary fat restriction. As another limitation, the lack of a control diet group must be mentioned. Third, this study was limited by the differences among the cases in the dosages of prednisone used, particularly the starting dosages (1–2 mg/kg/day), before dietary fat restriction because of the retrospective nature of the study. In addition, it is unknown whether efficacy was only because of dietary fat restriction because the dogs were receiving other treatments in addition to dietary treatment. Additional studies are needed to evaluate the efficacy of dietary fat restriction.

In conclusion, on the basis of this present study, dietary fat restriction appears to be an effective treatment in dogs with IL that are unresponsive to prednisolone treatment or experience a relapse of clinical signs and hypoalbuminemia when the dosage of prednisolone is decreased. In addition, dietary fat restriction may enable reductions in prednisolone dosage. However, this treatment requires further clarification to address unresponsive in IL dogs.

Footnotes

[a] Flagyl, Shionogi & Co, Ltd, Osaka, Japan
[b] Royal Canin, Inc, Aimargues, France
[c] Hill's Pet Nutrition, Inc, KS
[d] VQ-8142A flexible video endoscope, Olympus Medical System Corp, Tokyo, Japan
[e] VH-143-B25, Olympus Medical System Corp
[f] Prism 5 for Mac OS, GraphPad Software Inc, San Diego, CA

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