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Efficacy of oral AB070597 for the management of chronic kidney disease in cats: a prospective, randomised, controlled parallel-group study

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Sage

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Abstract

Objectives It has been reported that AB070597, which contains amino acids and peptides, may prevent the progression of chronic kidney disease (CKD) in cats. The aim of this study was to evaluate the effect of AB070597 on CKD in International Renal Interest Society (IRIS) stage 2 or 3 cats compared with a placebo.

Methods A prospective, randomised, controlled parallel-group study was conducted on 35 cats with CKD. The cats were randomly allocated to receive 300 mg of AB070597 or placebo for 180 days, and cats were re-examined every 30 days. Changes in the results were compared from baseline to endpoint in each group, and the efficacy of AB070597 in cats with CKD was assessed.

Results A total of 35 cats met the inclusion criteria, of which 20 received AB070597 and 15 received a placebo. Blood urea nitrogen (BUN), creatinine (Cre) and phosphorus levels increased significantly in the placebo group at 180 days compared with those at baseline, 30 days and 60 days, whereas these values were not significantly changed in the AB070597 group during the study period. The IRIS stage was also stable in cats with AB070597 from the baseline to the end of the study, whereas the IRIS stage progressed from stage 2 to stage 3 in 26% of cats with placebo. Body weight did not change significantly in either group.

Conclusions and relevance The administration of AB070597 in cats with CKD may be effective in preventing CKD progression.

Keywords: AB070597; amino acid supplementation; chronic kidney disease; renoprotective effect

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Introduction

Chronic kidney disease (CKD) is common in cats. CKD is a progressive disease, whose prevalence increases with age. The overall prevalence of CKD in cats is approximately 1.2–3.6%,[1,2] and increases to 22% in cats aged older than 10 years.[3] Approximately half of cats demonstrate stable CKD in the first year after diagnosis, whereas the other progress more rapidly with an increase in creatinine (Cre) of at least 25% from baseline during the same time period.[4] Currently, a specific treatment for CKD is lacking, and the standard care for CKD focuses mainly on slowing down its progression, preserving the remaining kidney function for as long as possible and maintaining quality of life.[5] Therefore, the management of cats with CKD includes supportive care, such as maintenance of hydration, diet management via phosphorus restriction, and curtailing of proteinuria and hypertension, anaemia and uraemia-related signs, such as inappetence and vomiting.[6] Even with these standards of care, some cats eventually succumb to CKD progression, and further options to prevent disease progression are warranted.

It is reported that AB070597, which contains amino acids and peptides including L-arginine, glycine, L-glutamine, L-histidine, L-aspartic acid, L-glutamic acid and L-carnosine, may prevent the progression of CKD in cats. In two studies, cats treated with AB070597 showed

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significantly decreased Cre and phosphorus levels from baseline with body weight remaining stable, whereas Cre and phosphorus levels increased significantly and body weight decreased in those not receiving AB070597.[7,8] Although the beneficial effects of amino acid supplementation in preventing CKD progression require further elucidation, treatment with AB070597 may be a promising option for managing cats with CKD.[7,8] Previous clinical trials were not prospective, placebo-controlled studies and used historical controls for comparison. Therefore, the aim of this study was to evaluate the effects of AB070597 in cats with CKD through a double-blinded, placebo-controlled, prospective, randomised study.

Materials and methods

Study design

This was a controlled, parallel-group study involving 13 veterinary practices in Japan to determine the efficacy of AB070597 in treating cats with stage 2 or 3 CKD based on the International Renal Interest Society (IRIS) staging system. The cats were randomised to receive either 300 mg of AB070597 twice daily or a placebo twice daily for 180 days. The blood and physical examination data were collected monthly. All owners provided written informed consent before the beginning of the study and were exempted from the expense for all diagnostics and test products. The entire study process was approved by an institutional ethics committee (approval number 20240630-1).

Animals

Privately owned domestic cats of various breeds with clinically stable CKD that did not exhibit obvious signs of dehydration upon physical examination were enrolled in this study. The cats remained under the care of their owners and the medical supervision of their veterinarians throughout the study. Cats were categorised according to disease stage using the IRIS staging system, based on their Cre levels at the time of enrolment. The continuation of formerly prescribed medications, such as antihypertensive drugs, cardiotonic agents, binding agents, prebiotics and probiotics, was permitted; however, any change in dose and dosage was restricted during the study period. Renal therapeutic diets and subcutaneous fluid therapy were permitted; however, no changes were allowed during the study.

Inclusion and exclusion criteria

Cats of all ages and breeds with clinically stable CKD were included. The following criteria were used to diagnose CKD: Cre levels ⩾1.8 mg/dl (exceeding the upper limit of the reference interval [RI]) and urine specific gravity (USG) ⩽1.035. Cats with Cre levels ⩾5.0 mg/dl were not included because of their general clinical instability. In addition, included cats exhibited elevated blood urea nitrogen (BUN) (⩾30 mg/dl) or displayed clinical signs consistent with CKD (such as chronic polyuria/polydipsia, small kidneys upon abdominal palpation or an imaging diagnosis). According to the IRIS staging guidelines, Cre in the range of 1.6–2.8 mg/dl or symmetric dimethylarginine (SDMA) of 18–25 µg/dl is defined as stage 2, and Cre in the range of 2.9–5.0 mg/dl or SDMA of 26–38 µg/dl is defined as stage 3. If there was discordance between IRIS stages for an individual cat when evaluating Cre and SDMA concentrations, the cat was assigned the higher of the two stages.

Cats were excluded if they had concurrent illnesses, such as diabetes mellitus, hyperthyroidism or neoplasia, and if their Cre levels decreased by more than half of the baseline value at 30 days, indicating that the previously increased Cre may have been due to acute kidney injury.

Supplementation

AB070597 was administered at a capsule dose of 300 mg twice daily. Each 300 mg dose included 25 mg of L-arginine, 50 mg of glycine, 50 mg of L-glutamine, 25 mg of L-histidine, 50 mg of L-aspartic acid, 50 mg of L-glutamic acid and 50 mg of L-carnosine. The placebo consisted of starch powder. Each dose was mixed with 1.5 ml of water and administered directly into the mouth of the cat or sprinkled onto a small amount of food fed to the cat.

Blood and physical examination

Blood samples were collected, and body condition was assessed when the cats visited the hospital on days 0, 30, 60, 90, 120, 150 and 180. The blood examinations included complete blood count (CBC), Cre, BUN, phosphorus, electrolytes and SDMA. After the collection of blood samples from each cat, a CBC was performed on site at each hospital and serum samples were refrigerated and sent to the Fujifilm VET laboratory for blood chemistry panels and IDEXX Laboratories for SDMA measurement. Urinalysis and blood pressure measurement were performed at days 0, 90 and 180. After urine samples were collected, USG was measured using a refractometer. Microscopic examination and dipstick testing were performed to screen for urine protein and urinary tract infection. Blood pressure was measured using a classical oscillometric unit because a high-definition oscillometric device, which is preferable for use in cats, was not available in Japan during the study period. The same blood pressure monitor was used consistently for each cat during the study. Cats were classified as having moderate hypertension (systolic blood pressure [SBP] 160–180 mmHg) or severe hypertension (SBP >180 mmHg) according to previously described criteria.[9] Body condition score (BCS) and muscle condition score (MCS) were recorded according to the American Animal Hospital Association nutrition and weight management guidelines.[10]

Data analysis and statistics

The sample size was based on information available at the time of the study and assumed that changes in BUN and Cre levels were similar to those observed in a trial of AB070597 supplementation for CKD in cats. Using these data (delta 0.4, SD 0.7), sample size estimation suggested a group size of 25 at an alpha of 5% and a beta of 0.8. Statistical analyses were performed using the StatMate V software (Atoms). Statistical significance was set at $P < 0.05$. The Kolmogorov–Smirnov test was used to determine whether the data were normally distributed. Because the data were normally distributed but not Cre in the control group, they are summarised as means ± SD. In the control group, Cre was not normally distributed, so it was log-transformed before subsequent analyses. This resulted in the normalisation of the data. Baseline data were compared between groups by the Mann–Whitney U, χ^2 or Fisher's exact test. For each group, the changes in Cre, BUN, phosphorus, potassium, packed cell volume (PCV), SDMA and body weight from baseline (day 0) to the end of the study (day 180) were compared using a repeated measures analysis of variance. Sex distribution, number of cats receiving each concomitant treatment and IRIS stage distribution were compared between the groups using the χ^2 or Fisher's exact test.

Results

Animals

A total of 47 owned cats were randomly allocated to the administered AB070597 group (AB group) or placebo group. Of them, 10 cats were excluded because of insufficient blood examination data or withdrawal by the owner (three and seven cats in the AB and placebo groups, respectively), and two cats were excluded because the Cre levels decreased by more than half of the baseline at 30 days, suggesting that these cats were suspected of having acute kidney injury (one cat each in the AB and placebo groups). Finally, 35 cats were included in the study: 20 in the AB group and 15 in the placebo group. The owners kept a daily log and reported that both AB and placebo were administered without any problems in all the cats.

The baseline data are shown in Table 1. The included cats comprised two intact and 18 castrated males, and two intact and 13 spayed females, with a mean age and body weight of 12.1 years (range 1–18) and 4.0 kg (range 2.38–6.3), respectively. At baseline, all cats exhibited clinical signs consistent with CKD, and 29/35 (83%) cats had an elevated BUN above 30 mg/dl. The USG remained below 1.035 in all cats both at baseline and during the examination period. The urine protein:creatinine ratio was not measured because urine protein was not detected using a dipstick analysis in any of the cats. No significant differences were observed in the signalment, baseline physical examination results or minimum database between the AB and placebo groups (Table 1). Three cats were classified as having moderate hypertension (two in the AB group and one in the placebo group), while three cats were classified as having severe hypertension (two in the AB group and one in the placebo group). All the cats were classified as IRIS stage 2 or 3 as follows: 13 and seven cats in the AB group and 11 and

Table 1 Population characteristics and blood examination of cats enrolled in the study at baseline

	AB group (n = 20)	Placebo group (n = 15)	*P* value
Age (years)	11.1 (1–18)	13.5 (5–17)	0.29
Body weight (kg)	3.92 (2.38–5.6)	3.99 (2.8–6.3)	0.61
Sex			0.24
Male intact	0	2	
Female intact	2	0	
Male castrated	10	8	
Female spayed	8	5	
PCV (%)	32.3 (12.3–48.4)	34.7 (16.3–53.7)	0.30
BUN (mg/dl)	44.0 (26.8–89)	44.6 (23–108)	0.77
Cre (mg/dl)	2.76 (1.8–4.3)	2.49 (1.8–4.4)	0.17
SDMA (μg/dl)	15.6 (8–23)	16.9 (11–41)	0.72
Phosphorus (mg/dl)	4.35 (2.8–7)	4.3 (2.7–8.4)	0.90
Potassium (mEq/l)	3.96 (3.0–5.0)	4.05 (2.9–5.2)	0.19
SBP (mmHg)	129.3 (91–191)	123.8 (81–202)	0.48
USG	1.018 (1.008–1.034)	1.016 (1.006–1.032)	0.71

Data are n or mean (range) unless otherwise indicated
P values were calculated within the Mann–Whitney U, χ^2 or Fisher's exact test
AB = AB070597; BUN = blood urea nitrogen; Cre = creatinine; PCV = packed cell volume; SBP = systolic blood pressure; SDMA = symmetric dimethylarginine; USG = urine specific gravity

Table 2 IRIS stage based on Cre or SDMA at baseline and 180 days of the AB and placebo groups

		AB group		Placebo group	
	Stage	Baseline	Day 180	Baseline	Day 180
Cre	1	0	2 (10)	0	0
	2	13 (65)	11 (55)	11 (73.3)	7 (46.7)
	3	7 (35)	7 (35)	4 (26.7)	8 (53.3)
	4	0	0	0	0
SDMA	1	13 (65)	16 (80)	12 (80)	10 (66.7)
	2	7 (35)	3 (15)	1 (6.7)	4 (26.7)
	3	0	1 (5)	1 (6.7)	1 (6.7)
	4	0	0	1 (6.7)	0

Data are as n (%)
AB = AB070597; Cre = creatinine; IRIS = International Renal Interest Society; SDMA = symmetric dimethylarginine

four cats in the placebo group, respectively. However, when the cats were classified based on SDMA, 13 cats were classified as stage 1, seven cats as stage 2 and none as stage 3 or 4 in the AB group, and 12 cats as stage 1, and one cat each as stage 2, 3 or 4 in the placebo group at baseline. Although one cat in the placebo group was classified as stage 4 based on an SDMA of 41 µg/dl at baseline (stage 3 based on a Cre of 4.4 mg/dl), the SDMA reduced to 16 µg/dl at the 30-day recheck (Cre 3.5 mg/dl) and remained in the range of 16–21 µg/dl during the follow-up period (Cre 3.0–4.0 mg/dl). Therefore, we regarded the baseline SDMA as an outlier and included the cat as CKD stage 3.

Overall, 25/35 (71.4%) cats were classified as stage 1 based on the SDMA, whereas no cats were classified as stage 1 based on Cre (Table 2). The distribution of IRIS stages based on Cre or SDMA levels did not differ significantly between the two groups.

Table 3 Concomitant treatment

	AB group (n = 20)	Placebo group (n = 15)	*P* value
Renal diet	10 (50)	6 (40)	0.55
Subcutaneous fluids	6 (30)	3 (20)	0.50
Darbepoetin alfa	0	1 (6)	0.24
ACEi/ARB	8 (40)	9 (60)	0.24
Pimobendane	3 (15)	1 (6)	0.44
Beraprost sodium	7 (35)	3 (20)	0.33
Amlodipine	1 (5)	1 (6)	0.83
Antibiotics	0	3 (20)	0.06
Binding agents	3 (15)	3 (20)	0.69
Others	1	1	
Famotidine, metoclopramide, mosapride, probiotics, iron supplement			

Data are as n (%)
P values were calculated within the χ^2 or Fisher's exact test
AB = AB070597; ACEi = angiotensin conversion enzyme inhibitor; ARB = angiotensin receptor blocker

Concurrent treatment

The number of cats that were fed renal therapeutic food was 11 (55%) and six (40%) in the AB and placebo groups, respectively, whereas other cats received commercial non-therapeutic diets. Regular subcutaneous fluid therapy was administered in six (30%) and three (20%) cats in the AB and placebo groups, respectively. Various drugs, such as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beraprost sodium and phosphorus-binding agents, were administered to some cats (Table 3). The number of cats receiving concurrent treatment and renal diet did not differ significantly between the two groups. None of the treatments was changed during the study period.

Transition of bloodwork

BUN, Cre and phosphorus levels increased significantly at 180 days compared with those at baseline and 30 and 60 days in the placebo group ($P < 0.05$), whereas no significant changes were observed throughout the study period in the AB group. In the placebo group, the mean ± SD of BUN, Cre and phosphorus at baseline and 180 days were 44.6 ± 22.4 mg/dl and 56.4 ± 29.6 mg/dl, 2.50 ± 0.71 mg/dl and 3.01 ± 1.07 mg/dl, and 4.3 ± 1.5 mg/dl and 4.9 ± 2.0 mg/dl, respectively, whereas those in the AB group were 44.0 ± 16.8 mg/dl and 45.4 ± 14.6 mg/dl, 2.76 ± 0.69 mg/dl and 2.72 ± 0.95 mg/dl, and 4.3 ± 1.1 mg/dl and 4.3 ± 1.0 mg/dl, respectively (Figure 1a–c). SDMA levels showed no significant changes in either group (Figure 1d).

In the AB group, PCV increased significantly at 90 and 180 days compared with at baseline ($P < 0.05$), and potassium increased significantly at 120, 150 and 180 days compared with at baseline ($P < 0.05$), although these changes were within the RIs. No significant changes

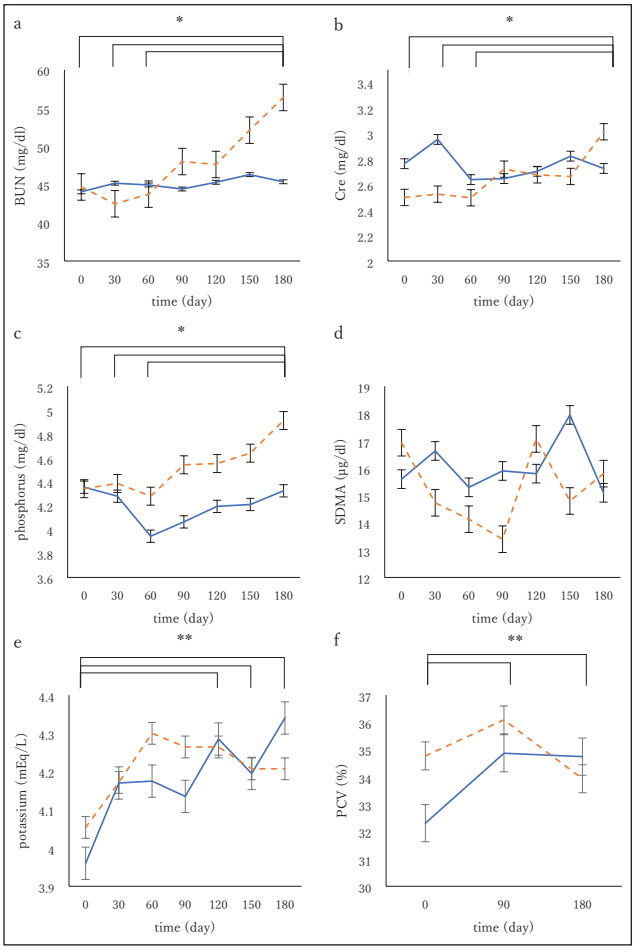

Figure 1 Changes of blood examination in the AB (solid line) and placebo groups (dotted line). Data are shown as mean ± SE. *Significant difference (P <0.05) in the placebo group; **significant difference (P <0.05) in the AB group. In the placebo group, BUN, Cre and phosphorus increased significantly at 180 days compared with 0, 30 and 60 days. In the AB group, potassium increased significantly at 120, 150 and 180 days compared with 0 days and PCV increased significantly at 90 and 180 days compared with 0 days. There was no significant difference in SDMA in each group. AB = AB070597; BUN = blood urea nitrogen; Cre = creatinine; PCV = packed cell volume; SDMA = symmetric dimethylarginine

were observed in the PCV or potassium levels in the placebo group (Figure 1e,f). In the AB group, the mean ± SD of PCV and potassium at baseline and 180 days were 31.6 ± 8.1% and 34.7 ± 7.6%, and 3.96 ± 0.50 and 4.34 ± 0.57 mEq/l, respectively, whereas those in the placebo group were 34.7 ± 8.9% and 33.9 ± 8.3%, and 4.05 ± 0.53 and 4.20 ± 0.67 mEq/l, respectively.

Transition of IRIS stage

According to the IRIS stages based on Cre and SDMA, most cats in the AB and placebo groups remained at the same stage from baseline to 180 days. In the AB group, the IRIS stage based on Cre decreased from stage 2 to stage 1 in 2/20 (10%) cats, whereas the IRIS stage advanced to stage 3 from stage 2 in 4/15 (27%) cats in the placebo group (Table 2, Figure 2).

Transition of body weight, BCS, MCS, USG and blood pressure

No significant changes in body weight, BCS or MCS were observed in any group during the examination period. The mean ± SD of body weight at baseline and 180 days in the AB group were 3.92 ± 0.86 kg and 3.95 ± 0.75 kg, whereas those in the placebo group were 4.1 ± 1.24 kg and 4.15 ± 1.17 kg, respectively. The number of cats with increased body weight at 180 days compared with at baseline was 12/20 (60%) in the AB group and 8/15 (53%) in the placebo group. There were no significant changes observed in USG within each group, and none of the cats displayed a USG above 1.035 during the examination period. In addition, no significant changes were observed in blood pressure within each group throughout the examination period. All the hypertensive cats had received amlodipine or telmisartan as anti hypertensive medication at baseline. The blood pressure of three severely hypertensive cats at baseline reduced to a range of moderate hypertension at the recheck. Therefore, based on the clinician's decision, the medication was not changed.

Discussion

This is the first prospective, controlled, randomised, parallel-group study to evaluate the efficacy of AB070597 administration in cats with CKD. Throughout the examination period, Cre, BUN and phosphorus levels did not show significant changes from baseline in the AB070597 group, whereas they increased significantly from baseline in the placebo group. In addition, no cats treated with AB070597 exhibited an advance to the next IRIS stage, whereas the IRIS stage advanced from stage 2 to stage 3 in 27% of cats in the placebo group. These findings suggest that AB070597 supplementation may prevent the progression of stage 2 or 3 CKD in cats.

The beneficial effects of amino acid supplementation on kidney disease have been demonstrated in previous clinical and experimental studies. In a human clinical trial, oral supplementation for 1 year of selective amino acids, including glycine, L-aspartic acid, L-glutamic acid, L-glutamine, L-histidine and L-arginine, arrested the progression of renal failure and improved hypercholesterolemia, albuminuria and hyperphosphatemia.[11] In studies on cats with CKD, Cre and phosphorus levels reduced persistently with AB070597 treatments, whereas non-treated cats showed a persistent increase in Cre and phosphorus levels during the 104-week study period.[7,8] Although the underlying mechanisms by which amino acids prevent CKD progression have not been fully elucidated, some amino acids have shown beneficial effects on kidney disease in experimental animal models. For example, arginine reduced renal damage, including

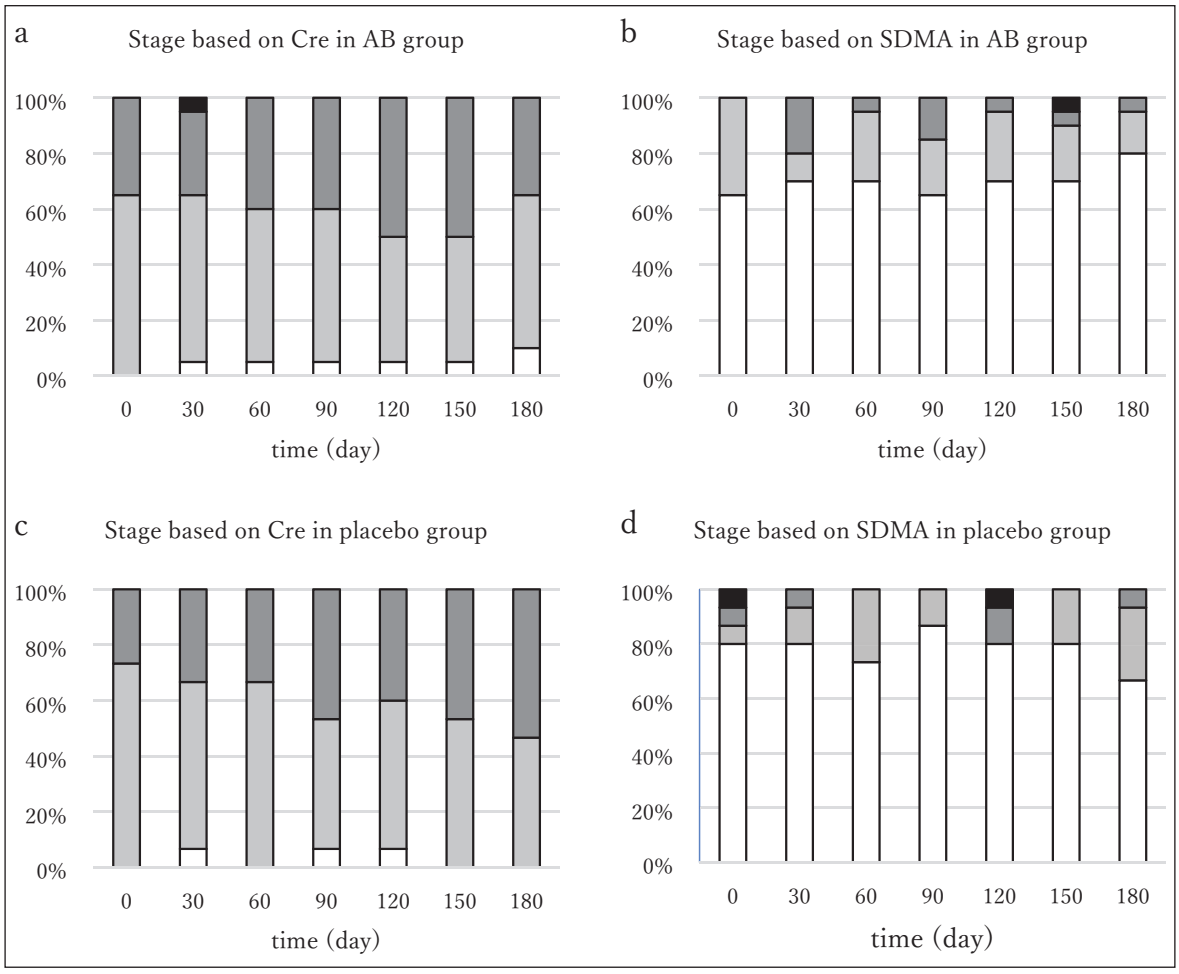

Figure 2 The proportion of the IRIS stage based on Cre or SDMA in the AB group or placebo group. Stage 1: □, stage 2: ■, stage 3: ■, stage 4: ■. Most of the cats in both groups are classified into IRIS stage 2 or 3 based on Cre, whereas cats in both groups are classified into IRIS stage 1 based on SDMA. Cre = creatinine; IRIS = International Renal Interest Society; SDMA = symmetric dimethylarginine

interstitial fibrosis, cellular apoptosis and macrophage infiltration in animal models of CKD experimentally induced via renal ablation or ureteral obstruction.[12,13] Oxidative stress is also an important factor in CKD progression. Patients with CKD show significantly higher oxidative stress levels than healthy controls even at an early stage, and oxidative stress markers are associated with CKD progression in humans.[14–16] In cats with CKD, urinary F_2-isoprostanes, biomarkers of oxidative injury, increased in the early stage of CKD compared with in cats with advanced CKD, suggesting that early antioxidative treatment may have a protective effect on CKD progression.[17] Some amino acids, including arginine,[12] glutamine,[18–20] histidine[21] and carnosine,[22] function as reactive oxygen species scavengers and reduce oxidative stress in animal models. Although the current study did not evaluate oxidative injury markers, it is plausible that the renoprotective effect observed in cats treated with AB070597, containing arginine, glutamine, histidine and carnosine, may be caused by a reduction in oxidative injury. Further studies are required to evaluate the relationship between AB070597 supplementation and oxidative stress in cats with CKD.

The potassium levels increased significantly compared with baseline in the AB070597 group without any drug or diet change during the study period, but not in the placebo group. Hypokalaemia is common in cats with CKD, affecting approximately 20% of patients.[23,24] Although the mechanism of hypokalaemia in cats with CKD is poorly understood, it may be caused by increased urinary loss owing to polyuria and tubular reabsorption decrease, because the most common pathological changes in cats with CKD are chronic tubulointerstitial nephritis and fibrosis.[25] In a previous report measuring renal clearance and tubular reabsorption rate, the renal clearance of potassium increased and the tubular reabsorption rate of potassium decreased significantly in cats with CKD compared with that in healthy control cats.[26] Although

the exact mechanism of increased potassium is unknown, it suggests that impaired tubular reabsorption of potassium was recovered in the AB070597 group.

PCV increased significantly from baseline by the end of the study period in the AB070597 group. Given the slight increase occurring within the RI, whether there was a clinically significant change and the underlying mechanism were unclear.

Body weight and muscle mass did not change in either group during the 6-month study period. Previously, the body weight of cats treated with AB070597 was stable, whereas cats in the control group lost a mean body weight of 0.9 kg during the 104-week study period.[7] The discrepancy in the body weight between the current and previous studies may be because the current study had a much shorter observation period (24 vs 104 weeks).

Unexpectedly, there was a huge discrepancy in the distribution of IRIS stages based on Cre and SDMA in the current study. The cats were diagnosed with CKD based on their history, elevated BUN and Cre, and decreased USG, and all cats were classified as IRIS stage 2 or 3 based on Cre. However, 25/35 (71.4%) cats in both groups were classified as IRIS stage 1 based on the SDMA. In addition, unlike BUN, Cre and phosphorus, SDMA levels did not increase significantly by the end of the study in the placebo group. SDMA has been considered a more sensitive marker for detecting decreased glomerular filtration rate (GFR) than Cre;[27] however, a recent study showed that the sensitivity and specificity of SDMA for detecting decreased GFR were comparable with those of Cre.[28] It is unclear why many cats were classified as IRIS stage 1 and why SDMA did not correlate with other blood parameters in this study because GFR measurements were not conducted, which was beyond the scope of the current study. Numerous promising biomarkers for evaluating kidney function in cats have been developed; however, their clinical benefits need to be evaluated and validated.[29] Until further studies provide more validated information, clinicians should evaluate kidney function and monitor CKD using multiple biomarkers.

This study has some limitations. First, the sample size did not reach the originally estimated number and was relatively small, which increased the likelihood of a type 2 error for all comparisons. Second, although the AB070597 dose used was determined based on the manufacturer's recommendations and previous reports,[7,8] the appropriate dose of the supplement must be validated. Third, concomitant treatment was not consistent in this report. Approximately half the cats received a renal therapeutic diet, while others received a non-therapeutic diet. Though there was no statistical difference in the number of cats receiving a renal therapeutic diet between the two groups, the different diets might have influenced the outcome. In addition, before this study, the details of treatments are unclear. Any changes in treatment just before the study period could have potentially impacted the results during the study period. Lastly, the observation period was only 6 months and the benefits of AB070597 on long-term outcomes, such as survival time, warrants further investigation.

Conclusions

BUN, Cre and phosphorus levels were stable in cats with CKD receiving AB070597, but increased in the cats receiving a placebo during the 6-month study period. These findings suggest that AB070597 effectively prevents disease progression in cats with CKD.

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Ethical approval The work described in this manuscript involved the use of non-experimental (owned or unowned) animals. Established internationally recognised high standards ('best practice') of veterinary clinical care for the individual patient were always followed and/or this work involved the use of cadavers. Ethical approval from a committee was therefore not specifically required for publication in *JFMS*. Although not required, where ethical approval was still obtained, it is stated in the manuscript.

Informed consent Informed consent (verbal or written) was obtained from the owner or legal custodian of all animals(s) described in this work (experimental or non-experimental animals, including cadavers, tissues and samples) for all procedure(s) undertaken (prospective or retrospective studies). No animals or people are identifiable within this publication, and therefore additional informed consent for publication was not required.

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