



leading to end stage disease. There is great similarity between human and feline renal architecture and function so it is possible to draw from the body of scientific information gathered concerning human renal disease and function and, with appropriate caution, apply those findings to cats.

Many pathways lead to renal disease. Certain lipoproteins induce the formation of reactive oxygen species (ROS) in glomeruli and in arteries. Antioxidants might prevent the damaging effects of these lipoproteins [9, 11, 17, 18, 20-25, 27, 33-35]. Progressive injury results directly and indirectly from angiotensin II receptors via mediators of angiotensin II-induced renal injury through transforming growth factor (TGF- $\beta$ ), fibroblast growth factor (FGF- $\beta$ ), tumor necrosis factor (TNF- $\alpha$ ) and platelet-derived growth factor (PDGF) [2-4, 6, 12, 15, 16, 30]. In addition, angiotensin increases oxidative stress, which causes a vasoconstrictor effect by increasing catabolism of nitric oxide (NO) [10, 13, 19, 20]. Aldosterone is also a major contributor in the progression of CRF [13]. All of these compounds promote the progression of CRF by enhancing cell growth, fibrosis and inflammation which destroy tubulointerstitial tissues and glomeruli [8].

Multiple approaches have been tried to prevent the progression of renal disease such as protein restricted diets, control of hypertension with angiotensin converting enzyme (ACE) inhibitors, diet substitution of saturated fats with polyunsaturated fats, immunosuppressants such as microphenolate mofetil (MME), corticosteroids such as prednisone [1, 14, 20, 31, 32] and morphogenic agents such as bone morphogenic protein-7 (BMP-7) [36]. None hold promises for halting or reversing disease progression with the exception of

BMP-7. Previous studies have shown that BMP-7 can reverse epithelial to mesenchymal transition in models of acute renal failure and can promote renal tissue repair[36]. Naked plasmids encoding feline BMP-7 could be employed to generate endogenous feline BMP-7 and thereby reverse renal disease[5], but government regulatory costs and restrictions would probably be prohibitive for veterinary applications.

The aim of this study was to discover whether AB070597, which according to the author's previous investigations, is a powerful ROS scavenger, a cytoprotective agent which reduces damage to proximal renal tubules and increases glomerular filtration rate (GFR), stimulates gluconeogenesis and suppresses proteolysis in skeletal muscle, has strong anti-inflammatory properties, is a precursor for NO production, and induces BMP-7 can halt the progression of CRF in felines. The criteria used to establish the cessation of progressive renal injury were 1) a halt to the rise of blood serum creatinine (CREA) concentration, 2) a halt to the rise of blood serum urea nitrogen (BUN) concentration, 3) a halt to the decrease in hematocrit (HCT), 4) a halt to the rise in blood serum phosphorus (PHOS) concentration, and 5) a halt to the decline in urine specific gravity (USG); and all for an extended period of time.

## **Methods and subjects**

An open-enrollment open-ended study format was selected so that patients, with confirmed CRF, could be added periodically. Patient owners were given informed consent forms for review and acceptance. Over a two year period, nineteen subjects with CREA ranging from 2.0mg/dl to 12.7mg/dl; with BUN ranging

from 20mg/dl to 152mg/dl; with HCT ranging from 21% to 46%; with PHOS ranging from 3.5mg/dl to 14.7mg/dl and with USG from 1.011 to 1.047, all on non-protein restricted commercial diets, received two 300 milligram oral daily doses of AB070597 as a dietary supplement. Doses were mixed with 1.5 milliliters of water and instilled directly into each subject's mouth or the dose was sprinkled directly on a small amount of food and fed to the subject. AB070597 was readily accepted without rejection. CREA, BUN, HCT, PHOS and USG measurements were made at varying intervals for each subject during the course of the study.

### Statistical Analysis

Each study subject served as their own control. Statistical comparisons were made by comparing measured parameters upon entering the study with measured parameters during and at the end of the study (Student's t-test; TexaSoft, WINKS SDA Software Ver. 6, Cedar Hill, Texas, 2007). Differences were considered statistically significant at  $P < 0.05$ .

### Results

The change in individual measured parameters is shown in Table 1. Mean CREA declined or had no statistically significant change in seventeen cats ( $P = 0.001, 0.001, [NS], [NS], [NS], [NS], [NS], 0.007, 0.001, 0.001, 0.001, [NS], [NS], [NS], 0.001, 0.001, [NS]$ ) and increased in two cats (Cat 5,  $P = 0.002$  and Cat 12,  $P = 0.001$ ). Of the two cats with increased CREA, Cat 5, started at 3.7mg/dl and ended at 4.0mg/dl. Study records show owner non-compliance in dosing with decreased or missed doses. Cat 12 started at 2.2mg/dl and ended at 2.7mg/dl. This cat had concurrent hyperthyroidism and was being

treated with methimazole upon entrance to the study. Its CREA values remained steady at 2.2mg/dl for the first twenty-four weeks of treatment and then rose to 2.6mg/dl at twenty-eight weeks, then rose to 3.5mg/dl at thirty-eight weeks but then declined to 2.6mg/dl at fifty-eight weeks after adjustments in its methimazole dose.

Mean BUN declined or had no statistically significant change in thirteen cats ( $P = 0.023, 0.001, 0.049, 0.002, [NS], 0.001, 0.001, [NS], [NS], [NS], 0.001, [NS], [NS]$ ) and increased in six cats (Cat 1,  $P = 0.001$ ; Cat 2,  $P = 0.009$ ; Cat 3,  $P = 0.001$ ; Cat 4,  $P = 0.001$ ; Cat 5,  $P = 0.001$  and Cat 12,  $P = 0.001$ ). Of the six cats with increased BUN, Cat 1 started at 35mg/dl and ended at 40mg/dl. The data support statistical significance but do not support practical significance. Cat 2 started at 126mg/dl and ended at 135mg/dl. Such high values are certainly clinically important. Study records show owner non-compliance in dosing with decreased or missed doses. Regardless of high BUN values, this cat regained its appetite, had improved coat and general aspect and gained weight (3.6Kg to 4.4Kg) by the end of the study. Cats 3 and 4 started at 20mg/dl and 23mg/dl respectively and ended at 27mg/dl. The data support statistical significance but do not support practical significance since both starting and ending values are within the normal reference range. Cat 5 started at 58mg/dl and ended at 61mg/dl. The data support statistical significance but do not support practical significance. Cat 12 started at 34mg/dl and ended at 47mg/dl. This cat had concurrent hyperthyroidism and was being treated with methimazole upon entrance to the study.

Mean HCT increased or had no statistically significant change in thirteen cats ( $P = 0.001, [NS], [NS], [NS], [NS],$

[NS], 0.001, [NS], [NS], [NS], [NS], [NS], [NS], and decreased in six cats (Cat 7, P = 0.017; Cat 8, P = 0.001; Cat 10, P = 0.019; Cat 13, P = 0.001; Cat 14, P = 0.001; Cat 17, P = 0.013). Of the six cats with decreased HCT, Cat 7 started at 46% and ended at 43%. The data support statistical significance, but not practical significance since both values are within the normal range. Cat 8 started at 32% and ended at 27%. The data support statistical significance, but do not support practical significance since both values are within the normal range. Cat 10 started at 41% and ended at 38%. The data support statistical significance but do not support practical significance since both values are within normal range. Cat 13 started at 24% and ended at 21%. The data support statistical significance. Cat 14 started at 41% and ended at 34%. The data support statistical significance but do not support practical significance since both values are within the normal range. Cat 17 started at 31% and ended at 28%. The data support statistical significance but do not support practical significance both values are within the normal range.

Mean PHOS decreased or had no statistically significant change in fifteen cats (See Footnote 1) (P = [NS], [NS], [NS], [NS], [NS], 0.001, 0.012, 0.007, [NS], 0.001, [NS], [NS], 0.001, [NS], [NS]) and increased in three cats (P = 0.001, 0.034 and 0.001). Of the three cats with increased PHOS, Cat 1 started at 4.2mg/dl and ended at 4.8mg/dl. The data support statistical significance but do not support practical significance since both values are within the normal range. Cat 4 started at 3.8mg/dl and ended at 4.1mg/dl. The data support statistical significance but do not support practical significance since both values are within the normal range. Cat 12 started at 4.1mg/dl and ended at 4.8mg/d. The data

support statistical significance but do not support practical significance since both values are within the normal range.

Mean USG increased or had no statistically significant change in sixteen cats (See Footnote 2) (P = 0.001, [NS], [NS], [NS], 0.001, [NS], [NS], [NS], [NS], 0.001, [NS], [NS], [NS], [NS], [NS], [NS]). No cat had a statistically significant decrease in USG.

The change in the sample population measured parameters is shown in Table 2. Sample population means of CREA, BUN, HCT, PHOS and USG showed no statistically significant change from study start to finish.

## Discussion

Each patient was monitored over the course of the study. Assessments were made for general body condition, weight change and ease of administration of AB070597. Blood serum biochemistry and hematology measurements were performed periodically by each patient's private veterinarian. There were no owner complaints or concerns regarding administration of the supplement; and surprisingly, many cats regarded direct oral administration (i.e. not mixed in food) as a treat. General body condition, including coat appearance and grooming habits, improved in each patient during the study, and most gained weight. Prolonged supplementation caused no adverse changes in hematology or blood serum biochemistry. There were no reports of gastrointestinal upset or diarrhea.

CRF is a progressive disease which ultimately leads to death. Any intervention that slows or halts the disease process would give hope in an otherwise dire situation. The very encouraging results of this study offer a foundation for such hope; with that

foundation based on the beneficial effects of the individual components of AB070597 described as follows:

Biomolecule 1 protects renal tissue from the negative effects of renal ischemia [37] and it facilitates the disposal of protein and metabolic waste, muscle metabolism, vascular tone regulation, immune system function and promotes the release of numerous hormones (glucocorticoids, growth hormone, prolactin, insulin, somatostatins, glucagons, catecholamines) through various pathways, whose disturbance can cause detrimental effects [37] on renal function. It also relieves a variety of pathological states including kidney hypertrophy and glomerular thrombosis [37].

Biomolecule 2 is produced in the mammalian body up to 50 times more than is taken in daily. Any decrease in its natural production is therefore of concern. The body uses it to form RNA, DNA porphyrin, bone collagen, glutathione, heme, bile, salts and for the detoxification and conjugation of toxic products, both exogenous and endogenous. It exerts a cytoprotective effect against anoxia, ischemia, heat, antibiotic, metals, and indomethacin induced kidney damage. It also increases the renal GFR, and thereby improves kidney function [37].

Biomolecule 3 is the precursor of nucleotides and proteins and is the substrate for and stimulates gluconeogenesis in all organs and tissues. It regulates carbohydrate metabolism and suppresses proteolysis in skeletal muscles and stimulates protein synthesis thereby counteracting the muscle wasting effects caused by CRF [37]. It too

is also an efficient reactive oxygen species scavenger [37].

Biomolecule 4 concentrates in the brain and has a regulatory effect on appetite and feeding behavior. It is readily available from food, but food intake is reduced in animals with CRF, thereby reducing the normal total cerebral amount. Supplementation helps to return appetite to normal status[37].

Biomolecules 5 and 6 are present in all tissues. They act as efficient reactive oxygen species (ROS) scavengers and thereby protect the kidneys from ongoing damage caused by reactive oxygen radicals [37].

Biomolecule 7 is the precursor for the substrate of bone morphogenic protein-7 (BMP-7). BMP-7 which has been shown in rigorous studies to reverse the epithelial to mesenchymal transition of kidney tissue [36, 37].

These encouraging results prove that AB070597 can halt the advance of chronic renal failure in felines when given as an oral supplement. Supplementation with AB070597 halted increases in blood serum creatinine, blood serum urea nitrogen and blood serum phosphorus concentrations; while at the same time halted decreases in hematocrit and urine specific gravity.

Table 1. Change in individual measured parameters over study duration (2 years).

Patient	CREA (mg/dl)	BUN (mg/dl)	HCT (%)	PHOS (mg/dl)	USG
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	Start-Mean SD	End-Mean SD (P)	Start-Mean SD	End-Mean SD (P)	Start-Mean SD	End-Mean SD (P)	Start-Mean SD	End-Mean SD (P)	Start-Mean SD	End-Mean SD (P)
1	3.2 0.16	2.5 0.60 0.001	35 1.75	40 11.00 0.001	26 1.30	32 6.30 0.001	4.2 0.21	4.8 0.88 0.001	1.022 0.001	1.026 0.004 0.001
2	8.7 0.44	7.6 0.90 0.001	126 6.30	135 1300 0.009	26 1.30	27 2.75 NS	10.5 0.52	10.9 0.56 NS	1.012 0.001	1.012 0.001 NS
3	2.3 0.12	2.2 0.17 NS	20 1.00	27 8.08 0.001	46 2.30	44 4.80 NS	3.8 0.19	3.9 0.21 NS	1.047 0.002	1.047 0.002 NS
4	2.5 0.12	2.4 0.23 NS	23 1.15	27 3.21 0.001	43 2.15	45 4.36 NS	3.8 0.19	4.1 0.49 0.034	1.045 0.002	1.045 0.002 NS
5	3.7 0.18	4.0 0.30 0.002	58 2.9	61 3.80 0.001	31 1.50	29 2.80 NS	4.4 0.22	4.5 0.80 NS	1.012 0.001	1.015 0.004 0.001
6	2.7 0.14	2.7 0.05 NS	43 2.15	40 4.60 0.023	34 1.70	33 2.30 NS	4.1 0.21	4.0 0.70 NS	1.020 0.001	1.020 0.001 NS
7	2.7 0.14	2.6 0.071 NS	60 3.00	49 9.60 0.001	46 2.30	43 3.10 0.017	4.6 0.23	4.3 0.40 NS	----- ----- -----	----- ----- -----
8	2.9 0.14	2.9 0.15 NS	49 2.45	46 6.1 0.049	32 1.6	27 3.5 0.001	4.1 0.20	3.3 1.0 0.001	1.018 0.001	1.018 0.0007 NS
9	12.7 0.64	11.4 1.80 0.007	152 7.60	134 26.20 0.002	21 1.00	26 6.60 0.001	14.7 0.74	13.3 2.00 0.012	1.011 0.001	1.011 0.001 NS
10	2.9 0.14	2.5 0.6 0.001	37 1.85	39 2.8 NS	41 2.0	37.5 5.0 0.019	4.0 0.2	3.6 0.5 0.007	1.017 0.001	1.016 0.001 NS
11	2.2 0.11	1.9 0.40 0.001	35 1.75	30 4.60 0.001	37 1.85	37 0.60 NS	3.5 0.18	3.3 0.90 NS	1.017 0.001	1.020 0.005 0.001
12+	2.2 0.11	2.7 0.50 0.001	34 1.70	47 9.10 0.001	42 2.10	44 2.90 NS	4.1 0.20	4.8 0.50 0.001	1.019 0.001	1.019 0.001 NS
13	4.9 0.24	3.8 1.00 0.001	102 5.10	77.7 21.60 0.001	24 1.20	21 3.60 0.001	8.1 0.40	6.9 1.10 0.001	1.018 0.001	1.018 0.001 NS
14	2.0 0.1	2.1 0.1 NS	58 2.9	60 3.5 NS	41 2.0	34 9.2 0.001	5.6 0.28	5.8 0.2 NS	1.019 0.001	1.019 0.001 NS
15	2.6 0.13	2.5 0.141 NS	42 2.10	40.5 2.10 NS	31 1.55	32 2.12 NS	----- ----- -----	----- ----- -----	----- ----- -----	----- ----- -----

Table 1 (Continued).

Patient	CREA (mg/dl)		BUN (mg/dl)		HCT (%)		PHOS (mg/dl)		USG	
	Start-Mean SD	End-Mean SD (P)	Start-Mean SD	End-Mean SD (P)	Start-Mean SD	End-Mean SD (P)	Start-Mean SD	End-Mean SD (P)	Start-Mean SD	End-Mean SD (P)
16	2.7 0.135	2.8 0.10 NS	53 2.65	50 4.90 NS	35 1.75	35 0 NS	5.0 0.25	4.7 0.40 NS	1.024 0.001	1.025 0.001 NS
17	8.7 0.44	5.9 3.90 0.001	141 7.00	95 64.40 0.001	31 1.60	28 5.00 0.013	14 0.70	9.5 6.40 0.001	1.015 0.001	1.015 0.0 NS
18	4.0 0.2	3.5 0.70 0.001	46 2.30	48 2.10 NS	39 1.95	40 0.70 NS	4.8 0.24	5.0 0.30 NS	1.019 0.001	1.019 0.0 NS
19	2.4 0.12	2.5 0.14 NS	46 2.30	46 0.71 NS	36 1.80	35 1.40 NS	3.7 0.18	3.7 0.0 NS	----- ----- -----	----- ----- -----

+ Concurrent hyperthyroidism .

Table 2. Change in sample population measured parameters over study duration (2 years).

CREA (mg/dl)		BUN (mg/dl)		HCT (%)		PHOS (mg/dl)		USG	
Start mean SD	End mean SD P	Start mean SD	End mean SD P	Start mean SD	End mean SD P	Start mean SD	End mean SD P	Start mean SD	End mean SD P
4.0	3.2	62	56	35	33	5.9	5.3	1.021	1.022
2.98	2.04 NS	40.11	31.59 NS	7.52	7.21 NS	3.52	2.46 NS	0.010	0.020 NS

#### Footnotes

1. Phosphorus measurements were not made in cat 15.
2. Urine specific gravity measurements were not made in cats 7, Cat 15 and Cat 19.

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