Effects of a Urinary Food Supplemented with Milk Protein Hydrolysate and L-tryptophan on Feline Idiopathic Cystitis – Results of a Case Series in 10 Cats

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ABBREVIATIONS

BCS	body condition score
BW	Body weight
EPA	eicosapentaenoic acid
DHA	docosahexaenoic acid
FIC	Feline idiopathic cystitis
FLUTD	Feline lower urinary tract disease
GAG	Glycosaminoglycan
LT	L-tryptophan
MPH	milk protein hydrolysate
QOL	quality of life

ABSTRACT

Case series summary. The effects of a urinary food supplemented with milk protein hydrolysate and L-tryptophan fed for eight weeks in eighteen household cats with feline idiopathic cystitis (FIC) are described. Cat emotional, quality of life (QOL) and taste perception scores were recorded every fortnight, as were feline lower urinary tract disease (FLUTD) signs. Eight cats did not complete the study due to various reasons (six of which were due to non-food related factors). In the ten cats that completed the study, FLUTD signs, cat emotional and QOL scores improved significantly during the study period. Taste perception of the food was rated excellent throughout the study.

Relevance and novel information. FIC is frequently seen in veterinary practice and is difficult to manage. Stress is a known risk factor in the development of FIC. At present, no studies of urinary foods with ingredients known to control anxiety in cats with FIC have been reported. This case series provides provisional evidence that such food improves both FLUTD signs and anxiety-related behaviours in cats with FIC.

INTRODUCTION

Feline lower urinary tract disease (FLUTD) is a collective term for cats showing one or more signs of pollakiuria, dysuria, haematuria, periuria or stranguria. Cats with FLUTD are commonly presented in general practice, with a reported prevalence of about 3-5%.[1,2] FLUTD can be caused by uroliths, urethral plugs, bacterial infections, neoplasia or

Table I. *Cat emotional and quality of life scores (mean ± SEM) in ten cats with FIC at enrolment (V_0) and 2 (T_1), 4 (V_1), 6 (T_2) and 8 (V_2) weeks thereafter.*

Parameter	V0 (Enrolment)	T1 (2 weeks)	V1 (4 weeks)	T2 (6 weeks)	V2 (8 weeks)
Contact tolerance with familiar people (scale 0 to 5)	3.3 ± 0.3	3.3 ± 0.3	3.7 ± 0.2	3.9 ± 0.2	4.2* ± 0.3
Contact tolerance with non-familiar people (scale 0 to 5)	1.4 ± 0.3	2.1 ± 0.4	2.2 ± 0.5	3.2* ± 0.5	3.3* ± 0.5
Aggression (scale 0 to 5)	4.2 ± 0.3	4.2 ± 0.3	4.4 ± 0.3	4.5 ± 0.2	4.5 ± 0.2
Other fears (scale 0 to 5)	2.3 ± 0.3	2.5 ± 0.3	2.9 ± 0.2	3.4* ± 0.2	3.7* ± 0.2
Quality of life (scale 1 to 5)	3.1 ± 0.2	3.8 ± 0.2	4.2* ± 0.2	4.2* ± 0.2	4.3* ± 0.2

**denotes significant difference ($p<0.05$) vs. V_0. For reasons of readability, only the significance of differences vs. V_0 are depicted. Emotional scores are on a 6-point ordinal scale (0 – high anxiety levels to 5 – low anxiety levels). The cat emotional score system is adapted from Beata.11 Quality of life is rated on a 5-point ordinal scale (1 - very poor to 5 - excellent). V = visit at clinic; T = telephone interview*

anatomical defects. However, in around 60% of cats with FLUTD no underlying cause can be found. This form of FLUTD is called feline idiopathic cystitis (FIC)[3] and is diagnosed by exclusion of other possible causes.

Several complex processes have been reported to play a role in the pathogenesis of FIC, such as reduced glycosaminoglycan (GAG) concentrations in the urinary bladder, increased urinary bladder and/or bladder wall concentrations of norepinephrine, nitric oxide, substance P, muscarinic and purinergic receptors, and/or mast cells (cited in [4]). These processes are reported to be involved in the neurogenic inflammation and increased permeability of the bladder wall. Buffington et al. (cited in [5]) described several imbalances in the sympathetic nervous system and the hypothalamo-pituitary-adrenal axis in cats with FIC, which may also play a role in its pathogenesis. In fact, this group postulated that chronic stress may be the underlying cause of these imbalances, leading to a variety of clinical signs, not only of FLUTD but also of gastrointestinal and skin disease.

Environmental enrichment and reduction in environmental stress have been shown to significantly decrease the signs of FIC in an uncontrolled non-blinded study.[6] Recently, a randomised controlled clinical trial showed that a dietetic urinary food, enriched with Ω-3 fatty acids (EPA and DHA) and antioxidants, decreased the rate of recurrent episodes of FIC signs in household cats.[7]

Positive effects of various nutrients and food ingredients on anxiety and stress-related behaviours in various mammals (including cats) have been reported, in particular of L-tryptophan (LT), an essential large neutral amino acid and of alpha S1 casein tryptic hydrolysate, a milk protein hydrolysate (MPH).[8,9] In a controlled, randomised study in cats from multi-cat households, Pereira has shown that cats in the LT supplemented group had significantly decreased displays of stress-related behaviours associated with anxiety and stress compared with the placebo group.[10] In another controlled, randomised study in cats with anxiety, Beata provided positive evidence for the efficacy of MPH in the management of cats exhibiting behaviours attributable to stressful social environments.[11]

Table II. *FLUTD-sign and overgrooming scores [median and (range)] in ten cats with FIC at enrolment (V_0) and 2 (T_1), 4 (V1), 6 (T_2) and 8 (V_2) weeks thereafter.*

Parameter	V_0 (Enrolment)	T_1 (2 weeks)	V_1 (4 weeks)	T_2 (6 weeks)	V2 (8 weeks)
Pollakiuria	3 (0-4)	1* (0-3)	1* (0-3)	0* (0-2)	0* (0-2)
Dysuria	3 (0-3)	0* (0-3)	0* (0-1)	0* (0)	0* (0)
Periuria	1 (0-5)	0 (0-3)	0 (0-2)	0 (0-1)	0 (0-1)
Haematuria	2 (0-4)	0 (0-3)	0 (0-3)	0 (0-1)	0 (0)
Stranguria	2 (0-3)	0* (0-3)	0* (0-2)	0* (0)	0* (0)
Overgrooming	3 (0-5)	0* (0-3)	0* (0-2)	0* (0-2)	0* (0-1)

**denotes significant difference ($p<0.05$) vs. V0. All scores are on a 6-point ordinal scale (0- no presence to 5 - severe presence). V = visit at clinic; T = telephone interview*

Despite the evidence that stress may be implicated in the pathogenesis of FIC and the results of above studies with LT and MPH on stress-related behaviours in cats, to the best of our knowledge no studies on the effects of a urinary food supplemented with these ingredients in cats with FIC have been reported. This report describes the effects of such food in a series of eighteen cats with FIC.

MATERIALS & METHODS

Cats showing signs of non-obstructive FIC within the two weeks prior to the study start date were recruited from feline specialty practices in Europe (two practices from England, Spain, and France, respectively and one from Poland). The diagnosis of FIC (i.e. excluding other causes of FLUTD) was based on the protocol in place at each individual practice and, for example, included urinalysis, urinary culture and diagnostic imaging of the lower urinary tract. Excluded were cats with major diseases that could affect the stress levels of these patients, such as hyperthyroidism, > IRIS stage 2 chronic kidney disease, gastrointestinal, pancreatic and liver disease, and cats that were treated/supplemented with drugs that could affect stress hormones, behaviour, or FLUTD signs, such as corticosteroids, non-steroidal anti-inflammatory drugs, antidepressants and antibiotics. The use of pheromones during the study was not excluded, provided this was initiated prior to the study start.

After enrolment, the cats were transitioned to the new food[a] supplied in white packaging and labelled as a urinary food supplied by Hill's Pet Nutrition over a one week period (see addendum I for key nutrients). Owners could choose the form to feed (dry, wet or a combination thereof). Daily feeding amounts were calculated by the practice based on the daily energy requirement for the relevant body condition score (BCS), using a 5-point scale. A thorough history was taken related to the environmental enrichment of the cat, and advice was given on how to improve the environment, following a protocol described by Buffington et al.[6]

At enrolment (V_0) and at repeat clinic visits after 4 (V_1) and 8 (V_2) weeks, body weight (BW) and BCS were recorded, as well as cat emotional scores (see addendum II for details of the scoring system), QOL (on a 5-point ordinal scale from 1 - very poor to 5 - excellent), FLUTD signs and overgrooming scores (on a 6-point ordinal scale from 0 – no presence to 5 – severe presence) based on owners' assessments of these during the 2 weeks before the respective visit. Taste perception of the food (on a 3-point scale – 1: refused the food; 2: needed some encouragement; 3: enjoyed the food) was recorded during repeat visits. The same data (with the exception of BW and BCS) were also recorded during telephone interviews by the practice at 2 (T_1) and 6

(T_2) weeks after enrolment.

Data are presented as mean ± SEM or median (range) where appropriate. The effect of time on each parameter was assessed using mixed model analysis of variance followed by Tukey's procedure for multiple comparisons (BW, BCS, cat emotional scores, QOL) and using Friedman's χ 2 test with the Wilcoxon signed rank test for two-way comparisons with adjustments for multiple comparisons using the Benjamini-Hochberg false discovery rate method (FLUTD signs and overgrooming scores), respectively. Statistical significance was set at $\alpha = 0.05$.

RESULTS

Eighteen cats entered the study. From eight cats, incomplete records were obtained; these were not included in the consolidated study results. Of these eight cats that did not complete the study, one cat owner stopped because of unrelated health issues (chronic kidney disease), two cat owners stopped feeding the food due to gastrointestinal signs during the transition period, two cat owners refused to further participate in the study although the cats were eating the food without any problems and for three cats no follow-up visits were scheduled because the attending clinician went on leave.

Complete records were obtained from ten cats (median age 5.9 years (range 0.8-12.4); all cats were neutered – five were female and five male. Nine cats were domestic shorthairs and one was a mixed domestic shorthair x Bengal. Seven had an exclusively indoor lifestyle and three a mixed indoor-outdoor lifestyle. Three owners chose to feed dry food only, seven owners chose a combination of dry and wet. Dietary history showed that prior to enrolment the cats had been on a variety of commercially prepared dry and wet maintenance foods. Only one cat had been fed a special dietetic food for urinary tract disease, but this was mixed with a maintenance wet food.

BW did not change significantly between visits (mean 4.6, 4.6 and 4.8 kg at V_0, V_1 and V_2, respectively), whereas BCS at V_2 was significantly higher than at V_0 (mean 3.1, 3.3 and 3.6 at V_0, V_1 and V_2, respectively). The cats' emotional scores are shown in Table I. Three out of four parameters measured and QOL as perceived by the owners improved significantly on the new food at some point in time. The cats' FLUTD sign scores are shown in Table II. Four out of five FLUTD sign parameters, as well as overgrooming improved compared with baseline at some point in time during the trial. The taste perception of both the dry (mean 2.5, 2.7, 2.8 and 2.7 at T_1, V_1, T_2 and V_2, respectively) and wet (mean 2.6, 2.7, 2.7 and 2.7 at T_1, V_1, T_2 and V_2, respectively) formulas was rated excellent throughout the study without significant differences between data points.

DISCUSSION

The results of this masked, uncontrolled study provide provisional evidence that a urinary food supplemented with ingredients reported to reduce stress-related behaviours in cats significantly reduces FLUTD signs and improves emotional scores and QOL in cats with FIC.

Although BW of the cats did not increase significantly, BCS at week eight was significantly higher than at enrolment. This is an interesting observation, because typically BCS is considered less sensitive than BW in tracking minor changes in nutritional status.[12] The increased BCS was due to two cats increasing from normal weight to overweight BCS, and three cats increasing from underweight to normal weight BCS. None of the cats had a decrease in BCS. The excellent taste perception scores are in line with these BCS changes. The fact that two cats showed an unplanned BCS increase underscores the importance of measuring daily feeding amounts and close monitoring of BW and BCS, since being overweight is an important risk factor in the development of FLUTD in cats.[13]

The improvements in cats' emotional scores are in line with those reported by Beata[11] in cats administered MPH and by Pereira[10] in cats on LT oral supplementation. The same scoring system and frequency

of interviewing were used as in the Beata study. The daily intake of MPH in Beata's study was 15 mg/kg body weight (BW) once daily. The daily intake by the tested food (15.3 mg/kg BW for dry and 15.7 and 15.4 mg/kg BW for the wet formulas for a 4-kg cat if fed according to the maintenance feeding instructions) was very similar to this study. One may argue that MPH may lose its stability and thus effectiveness during the manufacturing process of extruded pet food. However, it has been shown that MPH does not lose its stability even after intense and prolonged heat treatment.[b] Since pharmacokinetic data of MPH do not exist to date, it is not known whether once daily administration vs. multiple daily intake via the food may make a difference in effectiveness. In the LT oral supplementation study, Pereira used a different scoring system and the assessments were performed by trained observers, making a direct comparison more difficult. Moreover, in Pereira's study, only the added quantities of LT are known (12.5 mg/kg BW), and information about the amount of LT provided by the food is lacking. The added amount of LT in the test food was 12 (dry)-14 (wet) mg/kg BW when fed for maintenance. Assuming that the quantities of LT provided by the other food ingredients between the studies are similar, the total amounts of LT provided by the test food in this study may be equal or slightly higher than in Pereira's study. The FLUTD signs in this study were scored based on a global owner assessment of the signs in the preceding fortnight. Therefore, the results are difficult to compare with the results of other studies where FLUTD signs were rated daily by the owners, such as reported by Kruger et al,[7] who showed a decrease in FIC episodes from 11.2 (control food) to 1.3 per 1000 study days during a twelve months study in twenty-five household cats.

The study was performed in a daily clinical setting without tight control by a primary researcher, which inevitably resulted in some limitations. First, the diagnosis of FIC was not done in a standard fashion, but based on existing practice protocols. Second, FLUTD signs were assessed fortnightly rather than daily. Daily rating may be preferable as FIC is known to fluctuate frequently. Therefore, global fortnightly scores may underestimate the true incidence in FIC episodes. Third, only ten (55%) out of the eighteen enrolled cats completed the study. Most of these drop outs (6/8, 75%) were due to owner and practice related factors. Fourth, study duration was only two months. Although this time span may be appropriate to assess the effects on anxiety related behaviours, this period may be too short to assess a long-term sustainable effect on FIC recurrence. Finally, although masked (the attending veterinarians and owners did not know that the urinary food included ingredients known to reduce anxiety), the study was not randomised and was uncontrolled. Therefore, placebo effects, known to be significant in food and nutraceutical trials14 cannot be excluded.

CONCLUSIONS

To the best of our knowledge, this is the first published report showing, albeit in an uncontrolled fashion and in a case series, a positive effect of a urinary food supplemented with ingredients to control anxiety-related behaviours on signs of FLUTD and anxiety-related behaviours in cats with FIC. These findings need to be confirmed in a masked, randomised, controlled study with sufficient power and of appropriate study length.

SUPPLEMENTARY MATERIAL

Addendum I and II are tables with information about the nutritional contents of the foods and the cat emotional scoring systems, respectively.

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FOOTNOTES

[a] Hill's™ Prescription Diet™ c/d Urinary Stress dry and/or pouches (Salmon and Chicken), Hill's Pet Nutrition Manufactur-

Addendum I

[a] Hill's™ Prescription Diet™ c/d Urinary Stress key nutrients (as % dry matter base (DM) unless stated otherwise)

Nutrient	Dry	Pouch with Chicken	Pouch with Salmon
Protein	34.1	42.2	42.4
Fat	16.5	18.6	19.5
Carbohydrate (NFE)	42.9	31.2	31.4
Crude fibre	1.0	2.1	1.0
Ω-3 fatty acids	0.74	0.78	0.95
EPA + DHA	0.44	0.44	0.55
Ω-6 fatty acids	3.27	3.50	3.62
Vitamin E (mg/kg DM)	635	762	762
β carotene (mg/kg DM)	1.6	3.8	3.8
Magnesium	0.07	0.06	0.06
Phosphorus	0.69	0.62	0.81
Glucosamine (mg/kg DM)	1069	502	500
Chondroitin sulphate (mg/kg DM)	974	502	500
Milk protein hydrolysate	0.1	0.1	0.1
L-Tryptophan (mg/kg DM)	3,681	4,952	4,833
Target urinary pH	6.2-6.4	6.2-6.4	6.2-6.4

NFE: nitrogen-free extract; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid.

Addendum II

Cat emotional scores (adapted from Beata[11])

	0	1	2	3	4	5
Contact tolerance with familiar people	Can't be touched	Allows only short contact with humans when the cat initiates it	Does not tolerate long, provoked or spontaneous contact	Variable acceptance and seeking of contact	The cat regularly seeks and accepts contact – seldom refuses	Easily manipulated
Contact tolerance with non-familiar people	Disappears or is aggressive in the presence of people	Comes to observe but cannot be touched	Initiates contact after a while but does not accept being touched	Initiates contact after a while and accepts being touched	Accepts most, but not all human contact	Tolerant, friendly and playful with non familiar and familiar people
Aggression	Aggressive to familiar and non-familiar people, causing injury	Except for one person, aggressive to familiar and non-familiar people, causing injury	Possible but infrequent aggression that causes injury	Threatens without fleeing	Threatens and flees	Never aggressive
Other fears	Frightened by the slightest noise or any new stimulus	Unwilling to explore; responds in a fearful way to numerous stimuli	Exhibits fearful behaviour, but explores after a while	Frightened only by specific, known stimuli	Seldom frightened – calms down quickly	Never afraid

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[b] http://www.lactiumusa.com/pdf/restudy/ph-thermal-stability-lactium.pdf (15th October 2014)

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