Current Concepts in Clinical Nutrition

Ladan Mohammad-Zadeh, DVM, DACVECC

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Nutrition intersects all types of clinical conditions including cognitive dysfunction, heart disease, hyperthyroidism, renal disease, atopic conditions and cancer. The aim of this topic is to present current literature regarding nutrition as it relates to certain conditions in companion animals. It is not a comprehensive review rather a cross section meant to highlight those studies exhibiting high quality characteristics and have new information to offer.

The pet food industry has blossomed over the last 20 years. The increasing understanding of the role of nutrition in disease management has sparked a competitive market that is engaged in research development of therapeutic foods covering an ever-growing range of conditions. The number of Hills® prescription diets alone is large enough to have utilized every letter but 5 to name their products after.

The Association of American Feed Control Officials AAFCO serves as a forum for agencies involved in pet food regulation and enforcement such as the FDA and the USDA. As well it provides cross talk between regulatory agencies and those members in the pet food industry, agriculture and the NRC (National Research Council). AAFCO provides guidelines for industry and research regarding animal feeding practices, nutrient analytical techniques, ingredient quality assurance practices and provides accreditation to organizations who meet those guidelines. It is largely through the work of AAFCO and the NRC that the consumer has seen an increase in the diversity and quality of pet foods available in the US. The consumer demand for high quality pet foods, increased understanding of nutrition in disease management, and increasing lifespan of companion animals lends itself well to the growing research into therapeutic diets.

The Question of Nutrition

The topic of nutrition as it relates to pet health often starts in the exam room. No one doubts the value of obtaining a thorough nutrition history but the depth of information provided in the medical record can be variable. Thorough nutritional history should contain information on types of food given and amounts (including commercial and human foods), treats, eating habits, indoor/outdoor status, and exercise habits. Communications training is becoming a more integral part of veterinary education, recognizing that the right communication style can lead to a more open conversation between client and veterinarian. A 2015 study conducted by Martin *et al.* attempted to demonstrate this. They analyzed 284 videotaped veterinarian-client patient visits involving 17 veterinarians in companion animal practices in eastern Ontario, CA. Their goal was to examine the frequency with which nutrition was discussed, who initiated the conversation and how question phrasing influenced the response from the client. Only 172/284 (60%) visits contained conversation relating to nutrition and only 99/172 (57%) of these conversations were initiated by the veterinarian. The most frequent question phrasing was in

the form of a simple “what” question related to the diet. The most frequent response was describing the life stage or brand name of food. The next most prevalent phrasing was in the form of “yes” or “no” interrogative or declarative questions. The authors explained that both of these communication styles discourage the client from expanding on diet history. The recommendation was to phrase the nutrition question in an open ended manner such as “tell me about your pet’s eating habits” and then applying a funnel with “what” questions to get more details. The authors also described how certain words are more or less likely to elicit different answers. For example using the word “diet” instead of “food” or “foods” could determine whether the client offers information on treats or people food that the pet consumes. “What do you feed your pet?” could lead to a different answer compared to “what kinds of foods does your pet eat?”

These authors did not discuss the types of appointments (wellness check versus sick pet appointment) were involved. It is reasonable to suggest a veterinarian might conduct a more detailed inquiry of diet history when treating a pet with vomiting versus a healthy pet presenting for routine vaccines. Regardless, the analysis provided by Martin *et al*. could lead to better training regarding nutritional history taking.

Maybe z/d ® does stand for “zebra” diet!

The development of the novel protein diets has improved our therapies for not only primary inflammatory intestinal diseases but also for some forms of dermatologic disease. It is recommended to keep the pet on the strict new diet for a minimum of 8 weeks to evaluate efficacy. Failure of improvement during a diet trial can occur, usually prompting further diagnostics or change to a different novel protein diet. Ricci *et al*., in 2013 proposed that novel protein diets may actually contain undeclared animal DNA. They evaluated twelve commercially available canine dry limited ingredient diets (11 novel protein, 1 hydrolzyed diet) for the presence of material from animals not listed on the label. They were able to perform PCR and microscopy to detect major animal classifications (avian, mammalian, or fish) within the food samples. Only 2 of the 12 diets evaluated had microscopy and PCR analysis consistent with product labelling. Microscopy detected bone fragments from an unexpected class of animal in 10/12 diets sampled. The PCR test confirmed the presence of bone free ingredients such as fats and oils that cannot be seen via microscopy. This study could not determine the concentration of the contaminants or whether it represents a clinically significant protein source. However since there is still much to decipher regarding the link between diet and allergic disease, it is reasonable to scrutinize the possibility that a dog is not responding to a therapeutic diet trial because of contamination. The authors suggested the contamination likely occurs at processing plant where the rendering of the meat is done to obtain meat and bone meals.

Nutrition for Seizure Control

30 years ago it would have been unheard of to treat neurologic diseases like cognitive dysfunction or seizures with diet manipulation, but significant strides have been made in this area. Medium chain triglycerides (MCT) are increasingly becoming a topic of focus for its easy digestibility and health benefits for those with gall bladder disease and intestinal inflammatory disease. MCT are precursors to medium chain fatty acids which have a 6-12 carbon backbone. MCT can more readily be converted to ketone bodies which theoretically may be more easily utilized by brain cells. There have been several human studies indicating MCT can help with cognitive function and its ketogenic effect may help reduce seizure frequency in children with epilepsy. Nestlé Purina ® has funded research studies in dogs that suggested dogs fed a diet containing 5.5% MCT as fed improves cognitive function. One particular study of note is Law *et*

al., 2015 which assessed the effect of a similar diet on seizure frequency in dogs. This randomized, double blinded, placebo-controlled cross over study involved 21 dogs suspected to have idiopathic epilepsy. All dogs were on phenobarbital (PB) or KBr and had 3 or more seizures within the previous 3 months prior to study enrollment. Half of the dogs were fed the control diet and half of the dogs were fed the study diet (control diet + 5.5% MCT as fed). After 90 days each group switched to the other diet. They were followed for another 90 days. The results were indeed intriguing. Of the 21 dogs, 3 dogs were seizure free while on the MCT diet, 7 dogs had a 50% reduction in seizure frequency and 5 dogs had a 30-40% reduction in seizure frequency. 6 dogs had no change or an increase in seizure frequency. There were no changes in serum PB or KBr between groups. All chemistry values were similar between groups except for creatinine, which was lower in the MCT diet group, although creatinine was within the normal range for all dogs. There was no proposed explanation for this difference. There was an increase in serum beta-hydroxybutyrate as expected when on a ketogenic diet, however the increase in levels did not correlate with reduced seizure frequency. It is unclear why ketogenic diets reduce seizure frequency. Proposed mechanisms include altered brain energy utilization, altered neurotransmitter function, or unknown effect of MCT or ketones on anticonvulsant drug metabolism. This study design exemplifies what we should strive for in veterinary research. A study involving a larger population would be beneficial as well evaluating diet use in newly diagnosed epileptic pets.

Diet for Stone Dissolution

Lulich *et at.,* 2013 performed a prospect randomized clinical trial evaluating the efficacy of two low magnesium urine-acidifying diets in dissolving struvite uroliths in 37 cats. The cats were presumed to have struvite uroliths based on the presence of moderately radiopaque, round or discoid stones with smooth to slightly irregular contour. All cats had an initial urinalysis and only 6/37 had struvite crystalluria and 29/37 had no crystals noted. Cats were excluded if there was evidence of stones in the kidneys, ureter, urethra or if the cat had an obstruction, UTI, or was azotemic. 16 cats were fed Hills® s/d and 21 cats were fed Hills® c/d multicare. Radiographs, urine pH and other physical exam parameters were obtained weekly until stone dissolution. 5 cats that were fed Hills® c/d multicare did not have any reduction in stone size. The stones surgically removed in these cases. Four of these cats had 100% ammonium urate stones and 1 had 100% calcium oxalate stones removed. None of these “failures” had struvite stones, thus were not considered treatment failures. They were considered diagnostic failures because the criteria set forth to identify struvite stones did not correctly identify them as such. Other than the 5 cats with non-struvite stones, all cats achieved complete dissolution of uroliths. Mean time for complete dissolution for the s/d group was 13 d ±2.6 days (range 6 – 28 d) and for the c/d multicare group 27 d ± 2.6 d (range 7 – 52 d). Cats fed the s/d diet had significantly lower pH (6.083 ± 0.105) compared to c/d multicare group (6.431±0.109). The authors noted that larger stones took longer to dissolve. One of the cautionary notes regarding dissolution diets is the theoretical risk of urethral obstruction as the stones get smaller. None of the cats in this study developed urethral obstruction. Overall the authors were encouraged that if radiographic criteria regarding stone opacity and shape were met for struvite stones, that dissolution diet could be started. Since both groups achieved significant reduction in stone size by week 2, it was suggested that cats with uroliths that do not achieve 50% reduction in diameter by week 2 should be considered for surgery, as the stones were less likely to be struvite.

Effect of Diet on Feline Hyperthyroidism

Feline hyperthyroidism has been seemingly on the rise since its discovery in the early 1970's. There have been many etiologies proposed including age, geographic location, bisphenol-A coating in pet food cans, diets containing fish or soy as the main protein source, house dust containing PBDE (flame retardant) and iodine intake. In humans with nodular goiter (non-toxic thyroid hypertrophy), both chronic iodine deficiency *and* excessive iodine intake can lead to toxic nodular goiter (TNG); TNG is the human condition that is most similar to the clinical hyperthyroidism that is seen in cats. The research regarding the role of dietary iodine intake in the development of feline hyperthyroidism was compelling enough that the National Research Council reduced the minimum recommended iodine intake for kittens in 2007. Hills Prescription Diet ™ came out with an iodine restricted food in 2012. Y/d ® is an iodine restricted diet that was developed for the treatment of feline hyperthyroidism. It contains about half of the NRC recommendation for dietary iodine intake for cats.

Since its release in 2012, there have been only three notable studies on the effect of y/d ® diet on client owned cats. Van der Kooij *et al.*, 2013 conducted a multicenter prospective non-controlled open label study involving client owned hyperthyroid cats fed exclusively y/d® diet. They evaluated clinical parameters associated with hyperthyroidism (vomiting, PU/PD, polyphagia, elevated heart rate) as well as biochemical parameters (BUN, creatinine, total T4). Parameters were measures at the time of enrollment, week 4 and week 8. Of the original 225 cats enrolled, data from 88 cats was available at week 4 and only 68 at week 8. At week 4, 56/88 (63.6%) cats had normalized total T4. 32/88 (36.4%) cats continued to have total T4 above the reference range. At week 8, 51/68 (75%) had normalized total T4 and 17/68 (25%) had total T4 above the reference range. About half of the cats that continued to have elevated total T4 were reported to have poor palatability or had owners with poor compliance, whereas about 16% of cats that did achieve normalization of total T4 had poor palatability or owner compliance. The authors suggested that if palatability or owner compliance was improved that there may have been a better response in cats that failed to achieve a euthyroid state. There was improvement seen in clinical signs such as frequency of vomiting and PU/PD, however there was no difference in heart rate by week 8. BUN and creatinine were within reference range in all cats at the beginning of the study. There was no change in BUN, however there was a slight decrease seen in creatinine by week 8. Only one cat's total T4 dropped below the reference range but did not show signs referable to hypothyroidism. Although the authors noted all cats had a decrease in total T4 with y/d therapy (even those that did not achieve a euthyroid state), they did not include data indicating the degree of decrease of total T4.

Hui *et al.,* 2015 retrospectively evaluated 48 cats that were exclusively fed y/d® diet. Heart rate, body weight, BUN, creatinine and total T4 were evaluated before starting y/d® and then at 60 days and 180 days. At 60 days, 20/48 (42%) of cats had total T4 within the normal range. At 180 days, 39/47 (83%) had T4 within the normal range. 5/48 (10.4%) of cats had total T4 below the reference range at 180 days but none of these cats exhibited clinical signs of hypothyroidism. 3/48 (6%) cats had total T4 above the reference range at 180 days. None of the cats had a change in body weight or heart rate. Several cats were azotemic at the time of starting y/d® diet. There was a statistically significant decrease in BUN from enrollment (median 29 mg/dL) to 180 days (median 26 mg/dL). There was also a decrease in median creatinine from enrollment 1.8 mg/dL (range 0.4 – 4.9 mg/dL) to 1.5 mg/dL (range 0.4 – 3.3 mg/dL) at 180 days. Furthermore the authors proposed that the higher the total T4 was at the onset of diet change, the longer it would take for the total T4 to normalize.

Vaske *et al.,* 2016 conducted a prospective observational study involving 15 client owned cats there were fed y/d® exclusively for 6 months. In addition to total T4, blood pressure, renal parameters and body weight, the authors also examined GFR, SDMA, UPC and thyroid size. There were no changes noted in body weight, systolic blood pressure, GFR, SDMA, UPC or thyroid size. Although only 5/15 (33.3%) of cats achieved a euthyroid state at 6 months, all 15 cats achieved significant decreases in their individual T4 levels. Similar to the two previous studies, there was a decrease in serum creatinine seen at 6 months – although none of these cats were azotemic at the time of enrollment.

All of these study groups proposed similar reasoning behind the lowering of the creatinine; moderate protein restriction and high omega-3 fatty acid content which may be renal protective. The Vaske study was the only one to include thyroid gland measurements. Since the thyroid size did not change, it is possible despite a lowering of serum T4, these cats remain functionally hyperthyroid. This would account for no change observed in blood pressure, heart rate or body condition score across these three studies.

	Van der Kooij 2013	**Hui 2015**	**Vaske 2016**
N	88	48	15
Duration of study	8 weeks	25 weeks	25 weeks
Euthyroid at end of study	75% (out of 68)	83%	33%
T4 below reference range	1%	10%	0

Table 1. Side by side comparison of the main results of the hyperthyroid studies.

Based on these studies it is reasonable to consider an iodine restricted diet for the treatment of hyperthyroidism in cats. However the evidence regarding systemic improvement is conflicting. Only in one study were there observed improvement in PU/PD, polyphagia and vomiting. However this was not a blinded study, thus the placebo effect could account for the observed improvement. Two important systemic problems associated with hyperthyroidism include tachycardia and hypertension. Neither of these parameters improved with diet therapy. This was surprising given that most of these cats did achieve a euthyroid state. This leaves a bigger question as to whether or not these cats are still at risk for cardiovascular disease. None of the authors advocated the simultaneous use of drug therapy and diet therapy. Larger studies are warranted to assess the true systemic effect of diet therapy.

I chose to highlight these studies because of their prospective nature and some were blinded or double blinded. Although they were mostly small studies that warrant further investigation, the high quality nature of these studies gives them equal or more weight than larger retrospective, non controlled studies. They represent a cross section of topics, and not an exhaustive list. The most informative studies were easily found in popular veterinary journals but also surprisingly in journals that are less accessible such as the *International Journal of Applied Research in Veterinary Medicine* and *British Journal of Nutrition*. Pubmed and VIN are good resources for findings abstracts for veterinary related journal articles. It is important to stay

apprised on current research as we learn more about how diet affects health and disease, as this could change our clinical practice in the future.

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