The Science Of Cats
CHALLENGING PERCEPTIONS, CHANGING THE CONVERSATION.

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Are We Ready For Feline Genomic Medicine?

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Abstract
Genomic medicine (GM) is most often regarded as an emerging approach for disease treatment and prevention that attempts to account for the individual variability in genes, environment, and lifestyle of each person. The optimism is that this approach will allow doctors to predict more accurately which treatment and prevention strategies for a particular disease will work best individually or by ethnic groups of people. In this context, oncology is today at the forefront of practicing GM. Despite many advances in the use of GM, so far its practice is still very limited in human health. Nonetheless, the expectation is that the GM strategies that currently utilize individual human genome variant data for improving patient treatment will ultimately find a utility among veterinary clinics. If so, the question is how do we prepare for this eventuality of companion animal GM, in particular for a feline focus. We suggest three key resources are necessary: a high-quality domestic cat genome reference; sufficient sampling of sequence variation, all variant types across multiple cat breeds and random mixes; and finally an accessible community database for all queries anticipated of this variation data. Also, a review of the cats’ genetic history and how humankind has selected for various traits that shaped their genomes has provided clues needed to reach a higher understanding of the genetic origins of various feline diseases. In this brief overview, we highlight our efforts to bring GM to the veterinarian and preface it with the cats’ genetic history.

Studies suggest that the modern ancestors of today’s domestic cats spread from southwest Asia into Europe as early as 4000 B.C. The timing of domestication, however, is not clearly defined. The debate hinges on if cats merely enjoyed a beneficial relationship with humans, a self-domestication, or humans encouraged cohabitation by feeding cats while selecting for tameness, a human-facilitated (artificial) domestication (Figure 1). We can only estimate the timing and process, but it is clear no matter which domestication process was initiated, the need to control rodents that spread disease and consumed the stored grains was a common domestication motivation.

Archeological evidence suggests that cats were associated with human settlements during the period of the Fertile Crescent about 9,000 years ago. The Fertile Crescent is considered the birthplace of agriculture at which time wild grains and cereals were being propagated as well as the domestication of other animals, including cattle, sheep, and pigs. Today, most modern cats, approximately 74 million cats living in U.S. homes, are classified as random breeds, i.e., breed mixtures, while the fancier breeds that only number 44 are a tiny percentage of the total household cats.

With historical knowledge of cats’ domestication, several studies have attempted to discover their pattern of migration, the origins of modern breeds, and the unique molecular
signatures found in their genomes that were the result of artificial and natural selection. The modern breeds of cat originated as a process of their migration that started in southwest Asia into Africa and Europe and historically became further genetically admixed by human transportation as pets to multiple geographical regions, such as the Vikings bringing cats on their voyages.1,2 A comparison of domestic cat breeds to wild cats has shown few genomic regions to be under selection, but the genes within these boundaries are highly enriched for neuronal processes suggesting selection on tameness was a primary human motive in choosing cats for cohabitation.3 Also, this study highlighted the unique differences in the chemosensory gene repertoire between cats and dogs. While dogs retained a more substantial diversity of olfactory receptors for higher levels of odorant detection, cats have a higher number of intact pheromone receptors in support of their solitary lifestyles. All of these studies highlight the importance of detecting historical genomic selection as these genetic changes can reflect disease sequence variant origins and their frequencies, the latter a crucial filter in understanding a sequence variant’s health impact. To characterize the cat genomes unique variation features and relate these to a broad number of common and rare disease phenotypes, a crucial next step was to build the needed genomic resources if we are to practice GM.

As a computational instrument, the feline reference genome is a data model that sits at the center of nearly all genome and transcriptome analysis. It provides a coordinate system against which most other genomic data are presented. It also acts as a starting point for interpretation of newly sequenced genomes, both as a statistical prior and also as the default state of belief for heuristic algorithms. The reference is used to index variants in databases, perform cross-genome comparisons, and correlate genomic structure with annotation. A reference genome is a bridge between the newly discovered genome sequence of a given subject and the continually aggregating knowledge of the scientific community. We have built a high-quality domestic cat reference genome to serve as the central conduit for linking experimental knowledge from an immense accumulation of feline mutation signatures associated with numerous diseases, including cancer. Also, the conserved genome synteny of cat to the human allows us to gain valuable insight when seeking disease causal sequence variants (Figure 2). A majority (92%) of the Abyssinian female cat genome sequences are assigned to the known 18 autosomes and the X chromosome that ensures the use of a high-quality reference for the future implementation of feline GM.

Another resource essential for GM applications is a detailed knowledge of the sequence variants that are naturally segregating in domestic cats, either benign or harmful in their impact. In humans, large sequenced or genotyped cohorts have been characterized for estimates of their allele frequency and predicting the health consequences of each sequence variant type. Predicting the severity of each variant has been extremely challenging despite the application of complex computational data mining, such as machine-learning approaches. Anticipating the same sequence variant classification challenges in companion animals, we have started to evaluate the significance of variant diversity using deep individual sequencing methods, the 99 Lives Project (http://feline-genetics.missouri.edu/99lives), that currently has whole genome sequenced >200 cats of various fancier breeds, random bred, and wild cat origins. To date, we observe a large average number of single-base variants (SNVs),
9 million per unrelated domestic cat, with hundreds of these individual variants predicting the deleterious impact on protein function. Collaborative studies are ongoing to understand the future clinical implications of these newly discovered SNVs.

Summary
Companion animal GM is impending for veterinary medicine, but much data is missing to implement its practice in the clinic. The recently constructed standard reference of the domestic cat genome is a strong starting point for the discovery of disease variants, including cancer and common and rare diseases. Finally, our initial finding of total segregating SNVs and other variant types, e.g., deletions, their frequency of occurrence, predictive estimates of those posing a health burden, the population distribution of these variants, and all their known and inferred molecular properties will accelerate the reporting of successful cases of practicing GM.

References


Notes
Abstract
Although obesity is a risk factor for the development of diabetes in several species, including cats, most obese cats do not develop diabetes because they have developed protective mechanisms. However, in some cats, the protection fails and normal metabolism deteriorates. We will examine possible mechanisms that could act as a switch in the control of this process.

Introduction
Obesity, a Risk Factor for Type 2 Diabetes Mellitus
Obesity in cats and other species, including humans, is characterized by the accumulation of excess fat in white adipose tissue (adiposity) as well as in several other tissues. It was classified as a disease in human medicine in 2013, and likewise, was recently classified as a disease in veterinary medicine. In a recent Banfield study, one of three cats has been found to be overweight or obese. This is markedly higher than what was reported by the same group in 2010, when one of 10 cats was found to be affected. Overweight was the third most common recent physical finding in cats.

Most cats in the U.S. are neutered. Neutering increases the obesity risk due to a combination of decreased energy requirements and increased food intake. In cats fed ad libitum, an increase in food consumption was seen after neutering, whereas cats on a weight-maintenance regimen needed less food per kilogram of body weight (BW) to maintain the weight because energy requirements were lower. Eight and 16 weeks after neutering in male cats, but not in female cats, glucose administration led to a lower suppression of non-esterified fatty acid concentrations and higher concentrations of the adipokine leptin, suggesting increased insulin resistance and perhaps contributing to the increased risk of male cats to develop diabetes.

Excess weight is a well-known risk factor for type 2 diabetes mellitus. Environmental, genetic, and socioeconomic factors contribute to diabetes in humans and cats, so it is not surprising that concomitantly to the increase in fat mass, the prevalence of diabetes increased in the Banfield study. Between 2006 and 2010, the prevalence of diabetes in cats rose 16%, compared to a 32% increase in dogs. From 2006 to 2015, it rose 18.1% in cats, i.e., an additional 2.1% in a five-year period, and there were 67.6 cases/10,000 indicating perhaps a slowing of diabetes development in cats. For comparison, it rose 79.7% in dogs, and there were 23.6 cases/10,000.

The connection between feline obesity and diabetes mellitus is similar to what is seen in people. Obesity increases the risk for diabetes in both cats and people. However, one needs to consider that most obese humans or cats do not become diabetic. Some obese people remain metabolically healthy, i.e., they have a high body mass index (BMI) but normal metabolic and cardiovascular function, including normal fasting glucose and glucose tolerance. Their risk of progressing to diabetes is much less than that seen in people with the same degree of obesity and measurable metabolic abnormalities. The question that must now be raised is which factors are present in some, but not other, cats that may control the switch in metabolism leading to the progression from the euglycemic obese state to the diabetic state.

Inflammation has been suggested as an important pathogenic factor in the development of obesity-related diabetes in people. Little evidence exists to support that this is the case in obese cats. We have recently shown that concentrations in blood of inflammatory cytokines (IL-1, IL-6, TNFα) and catalase, superoxide dismutase, glutathione peroxidase, as well as urinary isoprostane concentrations did not change with the development of obesity. Other investigators also have not seen a change in blood and adipose tissue mRNA expression of TNF-α, interferon-γ, IL-6, and IL-10 in obese cats, though higher T-lymphocyte numbers, but not higher numbers of other inflammatory cells, were found in adipose tissue from obese cats in that study. The functional importance of this is unknown, since no difference in immune innate and immune adaptive response was documented when the immune function of obese cats were compared to lean cats.

Ralph DeFronzo, who won the Banting Medal for Scientific Achievement in 2008 for his outstanding research into the

Abbreviations
BMI: Body Mass Index
BW: Body Weight
EGP: Endogenous Glucose Production
HSL: Hormone-Sensitive Lipase
IVGTT: Intravenous Glucose Tolerance Test
LPL: Lipoprotein Lipase
TCA: Tricarboxylic Acid Cycle
VLDL: Very Low Density Lipoprotein
pathogenesis of diabetes in people, mentions eight culprits in the development of diabetes. The primary roles are played by the triumvirate of beta cells, muscle, and liver. It is well known that insulin resistance, i.e., a diminished cellular response to a given insulin concentration of muscle and liver, as well as beta cell dysfunction are necessary for the development of diabetes. Beyond these three, white adipose tissue, gastrointestinal tissue, pancreatic alpha cells, and brain also play a role.18

In this presentation, we will examine information from cat studies to provide a basis for discussion of how alterations in the function of the “triumvirate” and adipose tissue may play a role in the progression of feline obesity to diabetes.

The Role of Beta Cell Function in the Development of Diabetes

Maintenance of normoglycemia results from a balance between glucose production and disposal mediated by skeletal muscle, pancreatic beta cells, and the liver.19 In muscle, insulin increases glucose transport and glycogen synthesis. In liver, insulin activates glycogen synthesis, increases lipogenic gene expression, and decreases gluconeogenic gene expression. In white adipocyte tissue, insulin suppresses lipolysis and increases glucose transport and lipogenesis.

In cats, beta cell function, i.e., glucose-induced insulin secretion and glucose disposal, is for research purposes usually examined with an intravenous glucose tolerance test (IVGTT), because oral glucose tolerance testing, the preferred test in human medicine, shows high variability in cats,20 and the hyperglycemic clamp, another test used to examine the dynamic response of beta cells to glucose, is very labor intensive and has rarely been used in cats.21 The administration of the IVGTT entails the rapid injection of a large amount of glucose into the cephalic or jugular vein. This leads to a rapid response in insulin secretion, which is biphasic (acute short first phase, followed by longer maintenance [second] phase) with dosages higher than 0.3 g/kg. Blood samples for the measurement of glucose and insulin are collected at various intervals. The test is usually conducted for 120 minutes.

In a study using IVGTTs with different glucose dosages, no difference was seen in fasting blood glucose, 120 minute blood glucose, or glucose clearance in response to the administration of 0.3 to 1 g glucose/kg BW between obese and healthy, lean cats. A dosage of 0.8 to 1.3 g glucose/kg BW caused a lowering of the acute (first phase) response in obese cats. A dosage of 1.3 g glucose/kg BW also caused glucose intolerance in obese cats.22 Although the IVGTT is not the ideal test to examine insulin sensitivity, the fact that obese cats need more insulin to maintain glucose tolerance indicates that obese cats have insulin resistance. While it does not indicate which tissue is resistant, it is well known from other studies described below that obese, non-diabetic cats have insulin resistance in muscle and adipose tissue.

In support of these findings, in a longitudinal study of 20 cats that were fed ad libitum and became obese, no change in fasting blood glucose was seen, even with an increase in fat mass of 100%.15 Insulin concentrations increased until a 100% increase in fat mass was reached, when a blunting of acute phase insulin secretion and altered glucose clearance was seen. This indicates that extreme conditions (high degree of resistance and high glucose dose) are necessary before the response of the beta cell to glucose becomes abnormal. It also suggests that the increase in insulin with increased fat mass would be sufficient to overcome the resistance and maintain glucose concentrations under less “artificial” or “extreme” conditions, i.e., during the cat’s normal daily routine. This was illustrated by results from a study in which the glucose concentrations of obese and lean cats were monitored continuously for 156 hours with a continuous glucose monitoring system. The cats were fed every 24 hours. No significant difference in glucose concentrations was seen between lean and obese, indicating that not only fasting but also postprandial glucose was maintained in a group of cats with demonstrated insulin resistance and high insulin levels.23

Normal fasting blood glucose concentrations and high insulin have not only been shown in obese cats from well-controlled research colonies but also in client-owned obese cats.24-25 In fact, results from a recent study did not show a difference in routine hematological parameters, including fasting blood glucose or fructosamine concentrations among normal weight, overweight, and obese cats. Insulin concentrations, however, were significantly higher with higher fat mass, indicating higher insulin resistance. Insulin was much lower in naïve diabetic cats, and in >40% at the low end of the sensitivity range of the assay, suggesting beta cell failure.25

When insulin resistance was experimentally induced in cats whose beta cell mass had been surgically reduced,26 the progression of changes in the IVGTT glucose/insulin pattern could be followed from the normal to the diabetic state. The longer these cats were insulin-resistant, the lower the acute first phase of insulin and the higher the maintenance phase. Diabetes ensued when insulin secretion was approximately 80% of normal, likely because the beta cells became exhausted and were no longer able to maintain high levels of insulin secretion. These data also suggest that a reduced beta cell mass and function is required for the development of diabetes in insulin-resistant cats.

Hypersecretion of insulin is associated with hypersecretion of amylin, and this may be accompanied by the formation of amyloid, leading to more beta cell loss.27 Morphotometric
analysis of pancreatic islets suggests that amyloid leads to a reduction in beta cell volume; however, it is not thought to cause diabetes in the absence of other diabetogenic factors. Therefore, the authors of these studies suggested that destruction and replacement of beta cells by islet amyloid is not the primary diabetogenic event but may contribute to the progression by reducing beta cell reserve. The observation that islet amyloid in adult normoglycemic cats is associated with a significantly altered insulin secretion response after glucose stimulation may indicate that islet amyloid formation is linked to primary beta cell derangements in insulin secretion or degradation. Increased islet amyloid was also found in obese cats, perhaps a sequel to the high-insulin secretion. Contrary to the results of these studies, the amount of islet amyloid between healthy and diabetic cats was not different in a recent study.

When analyzing insulin secretion, one should not forget that a large proportion of insulin, but not C-peptide, is cleared by the liver before it reaches the circulation. Insulin is secreted into the portal vein, and the liver is exposed to twofold to threefold higher insulin concentrations than what is seen in circulation. Measurement of C-peptide is therefore a more precise measure of the amount of insulin that is actually released from beta cells. Because of the lack of a valid feline C-peptide assay, the true insulin secretion pattern is therefore not known. One also needs to consider that the extremely high dosages of glucose used in most IVGTTs (>0.5g glucose/kg BW) do not reflect the routine glucose concentrations seen by feline islets after a meal, and the results should not be applied to predict glucose homeostasis during the daily routine of a cat.

The Role of Muscle & White Adipose Tissue in the Development of Diabetes

Insulin regulates blood glucose concentrations through several mechanisms. In muscle, insulin promotes glucose uptake through the translocation of GLUT4-containing storage vesicles to the plasma membrane. The resultant increase in intracellular glucose enables increased glycogen synthesis. In white adipose tissue, it controls glucose uptake and lipolysis. In people, a multistage hyperinsulinemic-euglycemic clamp procedure, conducted in conjunction with isotopically labeled tracer infusions to measure substrate kinetics, can be used to determine simultaneously insulin action in muscle (seen as stimulation of glucose uptake from plasma), adipose tissue (seen as suppression of adipose tissue triglyceride lipolysis, i.e., glycerol and palmitate release into plasma), and the liver (seen as suppression of glucose output into plasma).

In cats, only a one-stage hyperinsulinemic-euglycemic clamp has been used to measure insulin sensitivity. It is assumed that the high concentration of insulin during the clamp is sufficient to completely suppress endogenous glucose production (EGP) by the liver and that there is no net change in blood glucose concentrations under steady-state conditions. Under such conditions, the rate of glucose infused is equal to the rate of whole-body glucose disposal or metabolizable glucose. The lower the amount of glucose that needs to be infused to maintain euglycemia under the hyperinsulinemic conditions, the higher the insulin resistance.

It was shown that the insulin sensitivity of obese cats was only approximately 40% compared to lean cats, and each kilogram of weight increase led to a decrease in insulin sensitivity of about 30%. The higher insulin levels of obese cats were therefore needed to overcome the effect of the loss of insulin sensitivity so that normal glucose control could be maintained. The higher insulin concentrations in obese cats were accompanied by a lower expression of the insulin-sensitive glucose transporter GLUT4 in both muscle and adipose tissue. Not surprisingly, GLUT1 expression, which is not insulin-sensitive, was normal. Although GLUT1 and GLUT4 are similar in structure, GLUT1 does not translocate to the plasma membrane in response to insulin like GLUT4, but it is localized in the plasma membrane and is responsible for basal transport of glucose.

In support of the GLUT4 data presented in the cat study, several investigators also found reduced levels of GLUT4 in muscles from obese insulin-resistant rats and in adipose tissue and normal blood glucose levels. The reduction in GLUT4 expression was accompanied by a reduction in insulin-stimulated glucose transport. Other studies in rodents and people have documented normal GLUT4 expression in muscle but lower expression in adipose tissue. However, GLUT4 translocation and/or function were abnormal in both and were thought to be an early defect in the development of diabetes. In our studies of cats, we also have found that the changes in glucose transporter expression in muscle and fat were very early derangements in obesity and occur before glucose intolerance was clinically evident.

One has to appreciate that insulin-stimulated glucose uptake is only about 5% in white adipose tissue compared to muscle in rodents and man. Thus, muscle insulin resistance is more important and plays a direct role in the development of hyperglycemia with insulin resistance.

Fat metabolism and fat distribution in white adipose tissue, muscle, and liver have been linked closely to the development of insulin resistance in people, so that insulin sensitivity is lower with higher abdominal (visceral [VAT] and/or subcutaneous [SAT]) fat deposition. A recent large cohort study indicated a gender difference: In men, abdominal SAT and VAT were associated with insulin resistance to a similar extent, whereas in women VAT particularly was associated with insulin resistance and insulin secretion. It is thought that intra-abdominal fat leads to increased flux of adipocytokines and hormones and has increased
lipolytic activity, which negatively influences insulin signaling. Others suggest that abdominal subcutaneous fat is more critical for changes in insulin sensitivity, in part due to its greater volume.

We investigated abdominal fat distribution in lean cats and also in obese cats before and after weight loss. With magnetic resonance imaging, it was seen that the total fat mass, as expected, was much larger in obese cats than in lean cats. However, in contrast to humans, the abdominal fat mass of cats was equally distributed between abdominal subcutaneous tissue and the intra-abdominal area, and there was no gender difference. Abdominal subcutaneous, intra-abdominal, and total fat correlated significantly with insulin sensitivity. Weight loss was associated with similar fat loss of subcutaneous and intra-abdominal fat and led to improved insulin sensitivity, suggesting that fat mass at both locations influences insulin sensitivity in cats.

Obese cats show dyslipidemia. High triglyceride, non-esterified fatty acid, as well as very low density lipoprotein (VLDL) concentrations were seen in obese cats in the fasted state. Free fatty acids can be derived from lipolysis of triglyceride-rich lipoproteins like VLDL, which is produced in the liver, or they can be released from adipose tissue (lipolysis). Fatty acid fluxes are primarily dependent on the activity of lipoprotein lipase (LPL) and hormone-sensitive lipase (HSL). We found that long-term obese cats had lower lipoprotein lipase plasma and fat activity and also lower mRNA levels compared to lean cats. Adipose tissue HSL expression was significantly higher in obese cats than lean cats, providing an explanation for the higher lipolysis of obese cats. The lower LPL activity might be due to the significantly higher level of tumor necrosis factor alpha (TNFα) expression in adipose tissue in obese cats compared to lean cats. TNFα is involved in the suppression of LPL, as well as in the suppression of adiponectin, an adipokine, which stimulates glucose uptake in muscle, adipose tissue, and liver, and activates fatty acid oxidation.

Adiponectin has been found to be lower in obese cats than in lean cats in our studies and in studies from other research groups. One group of investigators has seen lower concentrations of only the high-molecular weight form, while others have not seen a difference of total adiponectin. These changes account, in part, for the higher free fatty acid concentrations and dyslipidemia of obese cats. We have not examined LPL in the early stages of obesity, but studies in people have shown that LPL is increased early in obesity and decreases with longer-term obesity. Despite the dyslipidemia, obese cats do not develop atherosclerosis and are not at increased risk to develop cardiovascular problems. The lack of an inflammatory response to obesity in cats may contribute to their lack to develop cardiovascular problems and atherosclerosis in obesity and diabetes.

In contrast to the much lower activity of LPL in adipose tissue, muscle LPL expression was higher in obese cats and a significantly higher muscle/fat ratio was seen. These findings expectedly favor a partitioning of fatty acids away from adipose tissue toward muscle tissue. Higher myocellular lipid content, measured with magnetic resonance spectroscopy, was, indeed, documented in obese cats. In obese humans, skeletal muscle exhibits a reduced oxidation rate of fatty acids despite unchanged fatty acid uptake leading to increased lipid deposition. The increased partitioning of fatty acids into muscle is thought to negatively influence glucose transport. Increased muscular fatty acid uptake increases intracellular fatty acyl-CoA and diacylglycerol concentrations, which activate protein kinase PKC θ, leading to increased serine and decreased tyrosine phosphorylation of IRS-1. The result is a decrease in insulin signaling and insulin-stimulated glucose transport activity (Martins, et al.).

Role of the Liver in the Development of Diabetes

In liver, insulin stimulates glycogen synthesis, de novo lipogenesis, and protein anabolism and suppresses gluconeogenesis. The liver plays a crucial role in the disposal of exogenous glucose and in the control of endogenous glucose production. In order to better understand why obese cats with resistance to the effect of insulin in muscle and adipose tissue maintain euglycemia, we focused our attention on glucose metabolism in the liver in the search for factors that would explain why these cats, despite lower glucose transporter expression, maintain normal glucose control. A triple tracer protocol was performed in 24 overnight-fasted cats (12 lean, 3.5 ± 0.5 kg BW; 12 obese, 7.2 ± 1.1 kg BW, with equal gender distribution). Oral administration of [U-13C3]propionate was followed by an intravenous [3,4-13C2] glucose infusion. [3,4-13C2]-glucose was used to measure glucose turnover by conventional indicator dilution; [U-13C3]propionate was used as an anaplerotic tracer to measure fluxes through pathways associated with the TCA cycle. Blood samples were analyzed using nuclear magnetic spectroscopy. As seen in earlier studies, lean and obese cats had similar fasting blood glucose, but higher insulin concentrations were seen in the obese. The maintenance of normal glucose in obese cats in the fasting state was due to lower EGP. It was achieved through lower glycogenolysis (lower flux from glycogen to glucose) and gluconeogenesis (lower flux from glycerol to glucose and from phosphoenolpyruvate to glucose).

In a second study, we examined differences between obese cats and lean cats in the fasted and postprandial states. In that study, EGP was again lower in obese cats not only
in the fasted state but also in the postprandial state. In the fasted state, the low EGP was due to lower glycolysis. Postprandially, lower gluconeogenesis (lower flux from glycerol to glucose and from phosphoenolpyruvate to glucose) was seen in obese cats compared to lean cats. Plasma insulin concentrations, body mass index, and girth were negatively correlated with EGP. To our knowledge, glucose turnover and metabolic fluxes have not been evaluated in diabetic cats; however, it is known that diabetic cats are insulin resistant.67

Summary

These findings support the notion that obese cats are well equipped to combat insulin resistance. The beta cell increases insulin output matching the rise in insulin resistance until obesity is severe and a blunting in insulin secretion is seen. This early defect in insulin secretion is only uncovered when a large stimulus is used. The liver still maintains insulin sensitivity in long-term obese cats as indicated by decreased EGP allowing them to maintain euglycemia not only in the fasted but also in the postprandial state. Progressive beta cell failure has to occur as cats move from the insulin-resistant euglycemic phase to diabetes. Insulin secretion becomes lower not only during the early phase, the early indicator of beta cell failure, but also total insulin secretion eventually becomes erratic and low. This will lead to an increase in glucose concentrations with toxic effects not only on beta cells.

In beta cells, a reduction of beta cell mass occurs through glucose-induced hydropic changes as documented over 70 years ago68 and possibly through the formation of amyloid. Both lead to a reduction in beta cell mass. Dyslipidemia is present in obese cats and may contribute to the demise of beta cells. Although it has been shown in one study that hyperlipidemia produced by lipid infusion does not cause beta cell dysfunction in cats,69 one has to appreciate that it is very difficult to reproduce the lipid and fatty acid profiles that occur in obesity/diabetes with a commercial lipid infusion. Eventually the liver loses its sensitivity to insulin. This leads to an increase in endogenous glucose production resulting not only in impaired postprandial but also in high-fasting blood glucose concentrations. Fasting hyperglycemia defines diabetes mellitus and indicates that insulin action has become inadequate in the liver.69

A detailed discussion of the molecular mechanisms that underlie the changes that we have described is beyond the scope of this manuscript. However, the reader is referred to the excellent review by Max Petersen and Gerald Shulman.70

References


Notes
Notes
Taurine Deficiency Myocardial Failure In Cats — Science Or Serendipity?

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Introduction
Taurine deficiency-induced myocardial failure in cats and its reversal after taurine administration was the first evidence that taurine deficiency causes a clinically significant decrement in myocardial mechanical function. The path to this discovery, the aftermath, and the lessons learned are the topic of this presentation.

What Is Taurine?
Taurine (2-aminoethanesulfonic acid) is a sulfur-containing amino acid. Taurine is found throughout phylogenetic history, beginning with single-cell organisms. Among multicellular organisms, taurine is largely found in animals and is seldom encountered in plants.1

The majority of taurine is intracellular, dissolved in cytosolic fluid, and bound to cell membranes. Tissues with the highest taurine concentrations include the heart, retina, central nervous system, skeletal muscle,1 white blood cells, and platelets.2,4 High-tissue taurine concentrations are maintained by active transport from plasma to the intracellular space modulated by the β-adrenergic receptor adenyl cyclase system.5

Beyond conjugation of bile acids and detoxification of xenobiotics via conjugation and excretion in bile, the mechanism of action of taurine in mammals is not well understood. Taurine deficiency in cats results in retinal,6 myocardial, and reproductive dysfunction.1,7,8,9,10 Despite a multitude of in vivo and in vitro studies demonstrating a variety of biological effects in excitable tissues, several organs, and preparations, the mechanism for these effects remains unknown.

Science or Serendipity?
The road to discovering the cause and cure of the majority of cases of feline dilated cardiomyopathy (DCM) began when I was a veterinary student. As a second-year veterinary student at Cornell, I studied the pharmacokinetics of the calcium entry blocker verapamil in cats after reading reports of the drug ameliorating a condition in Siberian hamsters that looked clinically similar to feline hypertrophic cardiomyopathy (HCM).11 The results of my study suggested verapamil could not be effectively administered to cats as a safe chronic therapy. So much for curing HCM, though another connection later opened the door to demonstrating HCM is associated with a heritable genetic mutation in at least some cats.13 Fast forward five years to 1986. As a resident in cardiology at UC Davis, I decided that if I couldn't find a treatment for HCM, perhaps I could for feline aortic thromboembolism.

While researching this model of HCM, I came across papers reporting taurine having a similar ameliorative effect on this hamster disease model.12 I reached out to a young biotech company, Genentech. They were conducting clinical trials with a new clot-dissolving drug – tissue plasminogen activator (tPA). My pitch was, “I've got cats with clots. You have a drug that dissolves clots. Want to put them together?” They agreed. tPA proved an effective thrombolytic agent for cats, but the impact on survival was negligible. Many cats died during reperfusion. Those that lived did so at great effort and financial cost, only to soon re-thrombose and die.

The first patient we treated with tPA in the fall of 1986 was named El Blanco. He presented with a saddle thrombus secondary to DCM. He was treated with tPA, and his clot dissolved. Although we fought hard to manage his reperfusion-induced hyperkalemia, hours later he died. El Blanco's owner was devastated. She wanted an answer and asked great questions. Those questions together with El Blanco’s medical history opened the door to identifying taurine deficiency as the cause of most cases of feline DCM diagnosed prior to 1987. El Blanco had previously been seen by the UC Davis ophthalmologists for an unrelated problem. During that exam, El Blanco was found to have feline central retinal degeneration (FCRD), a relatively common finding in feline patients at the time.

While researching this model of HCM, I came across papers reporting taurine having a similar ameliorative effect on this hamster disease model.12 Appropriately, the UC Davis ophthalmologist asked what El Blanco eats. The answer, Hill's® Prescription Diet® c/d® Multicare Feline, was followed by the clinical assessment that because Hill's c/d is a “good food,” El Blanco’s FCRD must be caused by something else.

Always curious and wanting the best for him, El Blanco's owner asked what caused FCRD. The answer she received was taurine deficiency and a lot of other things. Appropriately, the UC Davis ophthalmologist asked what El Blanco eats. The answer, Hill's® Prescription Diet® c/d® Multicare Feline, was followed by the clinical assessment that because Hill's c/d is a “good food,” El Blanco’s FCRD must be caused by something else. In 1975, K.C. Hayes of Brandeis University near Boston published the association between FCRD and taurine defi-

Abbreviations
DCM: Dilated Cardiomyopathy
FCRD: Feline Central Retinal Degeneration
HCM: Hypertrophic Cardiomyopathy
NRC: National Research Council
tPA: Tissue Plasminogen Activator
ciency in cats. Because FCRD was so common in client-owned cats, the veterinary literature contained many references mistakenly associating FCRD with common conditions and interventions, such as ketamine administration.

Being the type of person to pursue every avenue, El Blanco’s owner wanted El Blanco’s blood tested. She found one of my soon-to-be colleagues and mentors, Dr. Quinton Rogers, who studied taurine nutrition in cats. In fact, his and his research partner James Morris’ work was the basis for the then-current published National Research Council (NRC) requirement for taurine in cat foods.

El Blanco’s plasma taurine concentration was lower than normal, but his diet was never changed nor was taurine supplementation administered. Knowing that El Blanco was taurine deficient, his owner asked if the clot that led to his demise could have been related to the taurine deficiency. I didn’t know the answer, but I remembered the papers suggesting taurine is important for cardiac muscle function.

At that time most cases of feline DCM were believed to be end stage and irreversible. Despite aggressive therapy, the average survival of a cat presenting with DCM in late October 1986 was 30 days.

Serendipity Strikes

The next week, three patients with feline DCM presented to our cardiology service. None had thrombi, but all three otherwise had presentations and histories similar to El Blanco. Each had DCM and FCRD and was eating Hill’s Prescription Diet c/d Multicare Feline prescribed by their veterinarian to prevent recurrence of lower urinary tract obstruction.

Blood submitted to Dr. Rogers’ lab documented taurine deficiency in all three cats. This seemed too much of a coincidence. I visited Dr. Rogers’ office to see what he thought. His response, to my surprise, was, “There is nothing to that story of taurine and the heart.”

At the time I didn’t understand the origin or significance of this peculiar response, but that would soon become clear. Still, Dr. Rogers kept an open mind and offered, “If you want to pursue this further, I have 11 cats in my colony that we’ve taurine depleted for four years. But, if you want to examine them, you’ll have to do it today because tomorrow we begin feeding them taurine.”

SERENDIPITY!

My cardiology mentors reluctantly let me borrow our only ultrasound machine, a behemoth of an M-mode machine, load it on a truck with a lift, and drive it to Dr. Rogers’ cat colony at the edge of campus. To everyone’s surprise, two of those 11 cats had DCM. Perhaps we were on to something.

In early December the first clinical feline DCM patient, named Cecil, was begun on taurine supplementation in addition to standard therapy (furosemide, captopril, and digoxin). Over the next several months, our group reported finding the presumptive cause and cure of the formerly incurable and deadly disease to colleagues at the ACVIM Forum, to the general veterinary community in DVM Newsmagazine (now dvm360), and to the world in Science. The cover of the Science issue containing the initial article honors El Blanco and Cecil. El Blanco is the white cat with heterochromia iridium, and Cecil’s before and after treatment m-mode echocardiograms are the background.

The period between our initial suspicion and submission for publication in Science was less than seven months (from late October 1986 to mid-April 1987). It was an exciting and frenetic time. It was also emotionally difficult. Advertising, running, analyzing, and writing up the initial clinical trial while being the only cardiology resident with a full clinical schedule, writing grants, getting married, and preparing to face the cardiology certifying exam and present our data at the ACVIM Forum in early June would have been more than enough.

Added to this were legal and other manipulations and threats from pet food companies trying to distance themselves, disbelief by the veterinary cardiology community, rejection by the taurine research community, and a struggle with the editors of Science over what we could share with colleagues prior to publication. I survived (and passed the exam) because of support from my colleagues, mentors clients, patients, friends, and family. They encouraged me to stand by the data and not let the naysayers reduce my confidence in the work. I would also like to recognize the Winn Feline Foundation for its flexibility and foresight in funding some of this initial research outside of their normal granting process.

Whirlwind, Corporate Deflection, Fraud & Disbelief

Whirlwind

I did not initially recognize the potential impact of our observations until I shared our findings with two physician colleagues, John Belizikian, my post-doc mentor at Columbia Medical College in New York City, and his friend, Russ Chesney. In December 1986, while I was in New York for my wedding, John encouraged me to put aside writing up the work I had done in his lab the prior year and focus on the taurine work. Russ, a taurine researcher himself, encouraged publishing in Science.

Corporate Defensiveness & Deflection

After returning from New York in early January 1987, I received an unexpected call from Hill’s Pet Nutrition. Although we felt it was premature to share with the veterinary community that our new and promising treatment for feline DCM was taurine (instead, we called it ND1244), we did tell the veterinary students rotating through the UC Davis cardiology service. One of the students shared the association with Hill’s Prescription Diet c/d Multicare Feline
with the practice where he worked during the holiday break, and a concerned practitioner called Hill’s.

Dr. Rogers received an urgent phone call. Three veterinarian executives from Hill’s insisted on coming to Davis to discuss our findings. Unfortunately, one arrived with a closed mind. He took the aggressive stance that this couldn’t be related to their diets and suggested, with impolite words, that our group was foolish and irresponsible for pursuing these investigations. After further unpleasant encounters, we insisted this individual not be present at future meetings. It makes me sad that a colleague would, under any circumstances, take this aggressive and close-minded tact. But only later would I learn how dishonorable, deceptive, and ironic his attitude and behavior were.

In the fall of 1987, I was invited to meet representatives from Taisho Pharmaceuticals, at that time the world’s largest manufacturer of taurine, who were in San Francisco for a scientific conference. During that meeting I learned that while Hill’s representatives were in Davis, trying to convince us of our errors, Hill’s had already ordered all the taurine Taisho had on hand and paid a huge premium to have it transported by air to Topeka, Kansas.

As other pet food companies were similarly implicated, we began receiving letters from their lawyers. I won’t go into further detail other than to state that recalling this response makes me sad. I am glad that after this and other incidents, including the melamine pet food incident of 2007, our colleagues at pet food companies have often opted to take a more collaborative and open-minded approach when veterinarians suggest there may be a problem related to diets.

**Fraud & Disbelief**

If not for serendipity and the open-mindedness of Dr. Quinton Rogers, my colleagues and I might never have pursued our initial hypothesis so vigorously. Quinton agreed to allow me to examine his taurine-depleted cats despite knowing about the recent scandalous retraction of a prior report of taurine deficiency causing cardiac dysfunction in humans. The retraction of this paper was part of what Forbes called the biggest major case of scientific fraud in cardiovascular medicine.

This historic misstep is relevant to this story for two reasons:

1. Despite the retraction of this paper and dozens of others by Darsee because data and patients were fabricated, it is impressive and a testament to the variety of reports, from the community of taurine researchers, that Darsee correctly postulated the clinical impact of myocardial taurine depletion upon myocardial function.
2. On a more personal level, after our group’s initial report on taurine deficiency-induced myocardial failure in cats, I reached out to the community of taurine researchers in hope of collaborating on future studies. To my surprise and disappointment, these overtures were initially rejected. After enthusiastically embracing Darsee’s report as validation of the clinical importance of their basic research on the role of taurine upon excitable cells and tissues, the researchers were not going to let a young veterinarian disappoint and embarrass them again. But seeing is believing. I challenged two taurine researchers with taurine-depleted feline colonies, K.C. Hayes and John Sturman, who worked at a neurologic research institute on Staten Island, New York, to allow me to travel to their labs with a portable ultrasound machine. After sharing data documenting that the ultrasound gel I used contained no taurine their taurine-depleted cats might consume, they agreed. Once they shared with the rest of the taurine community that myocardial function in a number of their taurine-depleted cats was reduced, the cynicism dissolved.

**What’s Happened Since?**

1. Colleagues in the veterinary cardiology community replicated and accepted that most cases of feline DCM were caused by taurine deficiency and reversible.
2. Our group reported more detail about the results of an expanded clinical trial.
3. Myocardial failure was induced in cats experimentally depleted of taurine and correlated with myocardial taurine depletion.
4. Experimentally induced taurine deficiency myocardial failure was reversed by supplementing with taurine.
5. A dramatic reduction in the incidence of feline DCM in the echocardiogram logs of two San Francisco Bay area radiologists during the two years after the reformulation of feline diets to contain more taurine in 1987 as compared to the incidence during the two years prior to reformulation.
6. Taurine deficiency was implicated in DCM in a colony of foxes.
7. Taurine deficiency myocardial failure and reversal was observed in Cocker Spaniels, Newfoundlands, Golden Retrievers, and Dalmatians.
8. Recent relationship of diet to DCM in dogs:
   - a. Is taurine deficiency a causative, confounding, or related factor?

**Some Unanswered Questions**

1. Why do only about 30% of cats depleted of taurine develop DCM?
2. Why are some diets with high concentrations of taurine depleting?
3. Why are some dogs susceptible to taurine deficiency?
4. What is the physiologic/physiochemical role of taurine in the heart and other excitable cells?
   I have theories, but no answers to the above questions. The last question is the one I’d most like to know the answer to.
What Does Taurine Do in the Heart?

Several mechanisms for taurine’s actions on the myocardium have been proposed. The three major theories are:¹⁷

1. Osmoregulation. Taurine is a small but highly charged osmotically active molecule. Changes in cellular osmolality induced by changes in intracellular taurine concentration have been proposed to be a protective mechanism in nervous tissue and myocardium.

2. Calcium modulation. Much of the available evidence supports a theory that taurine’s major effects on cellular function may be related to modulation of tissue calcium concentrations and availability.

3. Inactivation of free radicals. Inactivation of free radicals has also been proposed as a possible explanation for some of taurine’s actions.

Other proposed mechanisms specifically relating to myocardial function include N-methylation of cell membrane phospholipids,³⁴ direct effects on the contractile proteins,³⁵,³⁶ and interactions with the renin-angiotensin-aldosterone system.³⁷

One common thread I’ve noted in the literature describing acute effects of taurine is that the benefits of taurine are difficult to demonstrate in the absence of coincident stress upon the myocardium such as ischemia, oxidative stress, toxic insult, or calcium overload.

The best “answer” to “What does taurine do in the cell?” that I’ve heard or read is not my original thought and did not come from a publication. It was shared with me by the man I consider the father of taurine research, Ryan Huxtable, Ph.D.

Over 20 years ago, following a three-day taurine research conference, sitting in a bar outside Seville, Spain, after consuming many adult beverages, in response to that question, Ryan responded with a question, “What does water do in the cell?”

That unexpected (and unproven) response resonates true to me. I don’t discount that some organisms utilize taurine or taurine metabolites for osmoregulation or free radical scavenging systems. But it seems elegant and plausible that taurine, a zwitterionic molecule present intracellular in millimolar concentrations, does not bond to or incorporate into cellular structures nor have specific receptor sites, yet fills the literature with numerous experimentally demonstrable impacts upon cellular and organ function and results in clinically relevant pathology in the depleted organism, like water, by its physiochemical properties helps set the internal milieu within cells, facilitating normal metabolic processes.

References


Abstract
Taurine and carnitine are physiologically indispensable amino acid derivatives that may be acquired from foods. They circulate in homeostatically regulated micromolar concentrations but occur in low millimolar amounts in several tissues, notably cardiac and skeletal muscle. While deficiency and repletion observations indicate functional importance, physiological roles are incompletely understood, with physiology most elucidated for carnitine and many shortfalls in mechanistic knowledge for taurine. Significance of deficiency disease and reports of benefits of supraphysiological supplementations of taurine and carnitine continue to drive mechanistic investigations; these most commonly are studies of in vivo and in vitro models of deficiency, pharmacological antagonism, and gene manipulation.

Introduction
An objective of this review is descriptions of knowns and gaps in understanding about the physiological roles of taurine and carnitine that appear relevant to the nutrition and health of cats. An additional objective is brief coverage of the use of extraordinary supplementations of taurine and carnitine used in adjunctive treatments and mechanisms postulated for the benefit of cats. The focus is on cardiac and skeletal muscle, because taurine and carnitine are well known to be essential to the health of these tissues.

Taurine
Taurine is a quantitatively substantial amino acid with charged cationic and anionic groups, which at body pH is water soluble and a major intracellular osmolyte. Taurine occurs as a “free” amino acid in cardiac and skeletal muscle and many other tissues at millimolar concentrations. It may be concentrated in cells to 100-fold excess of concentrations in plasma. Taurine is positioned as an important physiological mitigator of cellular osmotic stress by virtue of its high intracellular concentration, active transporter-mediated uptake, and potential for rapid controlled release from tissues. Cardiac and skeletal muscle and other cells lacking taurine show major pathology to which is owed many functional roles discovered for taurine.

Study of cats has contributed largely to our understanding of the health significance of taurine. This work was notably prompted by findings in the 1970s of photoreceptor loss and retinal degeneration in cats given experimental diets. The diets caused a decline in plasma taurine concentration, which at the time was inexplicable because the diets were believed to be nutritionally complete. The retinal pathology and low taurine in plasma (as well in retina and other tissues) was not prevented by greater provision of methionine or cysteine.

Studies in subsequent years showed inadequate synthesis of taurine from sulfur-amino acid precursors in cats, thereby demonstrating a dietary requirement for taurine in cats. Recognition that cats can readily be made deficient of taurine by forgoing taurine supplementation well positioned cats for discovery of health consequences of taurine deficiency. Perhaps the most heralded of discoveries was identification of cardiomyopathy induced by taurine deficiency, and correction of the cardiomyopathy with taurine supplementation. Other noteworthy findings were deficits in reproduction and neurological development and function caused by lacking dietary taurine.

Taurine in Cardiac Muscle
Early efforts to identify the mechanistic underpinnings of taurine-deficiency cardiomyopathy were impaired by unexpected findings. A wide variance in sensitivity to disease caused by taurine deficiency was reported. A great and enigmatic influence of dietary matrix on inducing taurine deficiency was identified. Increasing dietary taurine concentration was reported to proportionally increase taurine in the myocardium of healthy cats, but in an apparent inconsistency, myocardial taurine concentration was observed to be greater in some cats with dilated cardiomyopathy (DCM) than in healthy cats given a taurine-free diet for a short period of time. Nevertheless, it was clear that DCM in cats

Abbreviations
ATP: Adenosine Triophosphate
Co-A: Co-Enzyme A
DCM: Dilated Cardiomyopathy
PDH: Pyruvate Dehydrogenase
ROS: Reactive Oxygen Species
SR: Sarcoplasmic Reticulum
TMNO: Trimethylamine N-Oxide
with low plasma taurine could be corrected with oral administration of taurine and that incidence of DCM diminished when taurine supplementation was increased by cat food manufacturers. The taurine deficiency of cats appeared to cause progression of abnormalities, with initial stages associated with diastolic defects and systolic dysfunction in severe cases of DCM.

Demonstration of myocardial disease induced in cats by dietary lack of taurine compelled investigators in the 1980s to begin study of physiological roles for taurine in the heart. Rat and much later arriving mouse models in place of cats were increasingly used, as study of them was more ethical, cost efficient, and expedient for testing hypotheses. Unfortunately, dietary-induced taurine deficiency could not be achieved in rodents. When given a taurine-free diet, rodents readily synthesize taurine from methionine and cyst(e)ine obtained from food. Studies with inhibitors of taurine transport, murine knockout models, and a variety of in vitro tissue and cell culture preparations since have been informative. However, though much understanding has been gained, gaps remain in mechanistic details of taurine’s role in cardiac physiology.

Several deficits of taurine deficiency are described. These have been recently reviewed by Schaffer and Kim. Among these are impaired contraction of myocardium resulting from taurine-sensitive conditions. A detrimental change in intracellular calcium dynamics is postulated through a slowed reuptake of calcium by sarcoplasmic reticulum (SR), which is suggested to be responsible for slowed myocardium relaxation and diastolic dysfunction in DCM. Reduced calcium sensitivity of myocardium contractile proteins secondary to taurine depletion may contribute to the systolic dysfunction observed in DCM. Low taurine is associated with increased phosphorylation of troponin I, which consequentially negatively affects calcium sensitivity of contraction. Low taurine also is associated with diminished available adenosine triphosphate (ATP) for myocardium contraction, putatively through decreased sarcoplasmic reticulum Ca2+ ATPase activity.

With respect to energy available for contraction, taurine deficiency adversely impacts mitochondrial function and integrity. The mechanism is not clear but may be a lacking of taurine for synthesis of specific tRNA (the wobble uridine of tRNA\text{Leu[UUR]}) required for mitochondrial protein synthesis. Lowering taurine increases intracellular production of reactive oxygen species (ROS), which is suggested to be caused by uncoupling of mitochondrial redox activity. Resulting oxidative stress and lacking energy may lead to myocardial cell osmotic stress, mitochondrial autophagy, and apoptosis. Deficiency of taurine in osmotic stress would be especially detrimental. Flux of taurine into and out of cells is demonstratively protective of damage against changes in cell volume from osmotic stress.

External to the heart, angiotensin II and norepinephrine mediate changes in the structure of a failing heart. They stimulate protein synthesis, which initially improves cardiac function, but they also promote cardiomyocyte apoptosis and ventricular remodeling. Taurine supplementation may lessen negative effects of these factors.

**Taurine in Skeletal Muscle**

The largest body pool of taurine resides in skeletal muscle. An abundance of taurine is required for normal calcium homeostasis in skeletal muscle, notably for adequate calcium reuptake by SR. Study of taurine transporter knockout models show exercise performance is diminished when skeletal muscle taurine concentration is reduced by 90%. Accompanying the low taurine is muscle atrophy and necrosis and shifting from oxidative to glycolytic metabolism. The metabolic shift is suggested to be related to mitochondrial dysfunction.

Like with cardiac muscle, taurine supplementation will drive an increase in muscle taurine concentration. Correspondingly observed are increased contraction force, improved resistance, and recovery from fatigue. The effect is thought to be a result of taurine affecting greater calcium storage in muscle and availability during contraction.

A decline in muscle taurine concentration is observed in aging humans. Rodent studies show that age-related changes in skeletal muscle are similar to those invoked by taurine deficiency. These findings should prompt investigation into a positive role that taurine supplementation may have in sarcopenia of aging.

**Carnitine**

Carnitine is like taurine in many ways; it is an endogenous, small, organic, zwitterion that occurs in cardiac and skeletal muscle and many other tissues in varying but high concentrations relative to plasma. Specific and saturable transporter activity uptakes carnitine. Once carnitine is intracellular, the molecule may be exported free or as a fatty acid conjugate to reenter plasma. A substantial amount of carnitine is esterified to fatty acids of varying kinds, which is unlike taurine, a mostly unbound amino acid with a diversity of small pools where it is bound in compounds like bile acids and taurine chloramine.

Carnitine like taurine may be obtained from diet but is also synthesized, mostly in liver with some contribution by kidney and some brain synthesis. Carnitine acquired from food (e.g., meat and dairy products) appears to be substantial and account for about 75% of the carnitine in humans. However, systemic bioavailability is only 5 to 15% of an oral dosage in humans. With dietary ingestion, bioavailability is much higher, 54 to 86%. Parenteral administration is reported to acutely affect concentrations in tissues depleted of carnitine. Carnitine is also formed de novo; it is a dietary
amino acid derivative, requiring lysine and methionine for its production, the former for carbon backbone, the latter for methyl carbon on the trinary amine. Reportedly 95% of carnitine is found in the heart and the skeletal muscle.

Carnitine Physiology

Physiological essentiality of carnitine is supported by pathological descriptions of hepatic steatosis, hepatomegaly, hyperammonemia, skeletal myopathy, and cardiomyopathy in primary carnitine deficiency. A fundamental physiological role of carnitine is well established and appears to be consistent across tissues. The main function of carnitine is that of a cofactor of enzymes, which together shuttle fatty acids across the inner mitochondrial membrane of cells. The shuttling is bidirectional, with carnitine entering the mitochondrial matrix as acyl-carnitine and leaving the matrix as acetyl- or free-carnitine. Fatty acids entering the matrix as acyl-carnitine first are esterified to Co-enzyme A (Co-A), a derivative of vitamin B5 (pantothenic acid). Thereafter, they are oxidized by length-specific fatty acid dehydrogenases in the pathway of β-oxidation to acetyl-Co-A, which in turn is oxidized to carbon dioxide and water to yield reducing equivalents that drive oxidative phosphorylation and production of cellular energy as ATP.

Intuitive to understanding the importance of carnitine to fatty acid metabolism is appreciation that cellular energy and all cellular processes that depend on ATP production may be limited by availability of carnitine. While it is true that cellular energy can be obtained from glycolytic metabolism, most ATP in cells is formed from the oxidation of fatty acids. The healthy functioning heart is estimated to derive 70% of its energy from oxidative metabolism, the bulk of which comes from catabolism of fatty acids.7

Carnitine has an additionally established role in intermediary metabolism. Abundance of carnitine may indirectly affect energy derived from glycolytic metabolism and accumulation of glycolytic products that are metabolic acids, i.e., pyruvic acid and notably lactic acid. Abundance of carnitine will affect the concentration ratio of acetyl-CoA and free CoA in the mitochondrial matrix. Low carnitine allows a consequential buildup of acetyl-CoA and a lowering of free CoA in the mitochondrial matrix. Such a condition affects glycolytic metabolism in the cytoplasm of cells though inhibition of pyruvate dehydrogenase (PDH), an enzyme complex located on the inner mitochondrial membrane. Activity of PDH controls the rate of glycolysis upstream and activity of the citric acid cycle downstream. Diminished activity of PDH will lower flux of reducing equivalents for forming cellular ATP. Therefore, deficiency of carnitine may interfere with complete oxidation of glucose and thereby deplete mitochondria and the entire cell of energy. Further, carnitine deficiency may impose an acidosis and osmotic stress from accumulation of lactic acid developed from incomplete glycolytic metabolism.

With adequate diet, in health, and without stress, deficiency of carnitine is suggested unlikely. Deficiency and excess appear defended against by homeostatic regulation of carnitine modulation of dietary uptake, transport into and out of tissues, and urinary excretion. Nevertheless, in pathological conditions known to cause secondary carnitine deficiency, benefit of supplementation is empirically supported, though the degree of benefit varies.

Carnitine in Cardiac Muscle

Myocardium well extracts plasma carnitine; it maintains a 60-fold concentration gradient against plasma. Adequate carnitine is essential for normal myocardial function, most clearly through its role in glycolytic and oxidative energy metabolism. In heart disease resulting in ventricular dysfunction, carnitine in myocardium decreases. Supraphysiological carnitine supplementation of humans reduces the concentration decline and modestly to moderately improves heart function and symptoms of heart failure. The benefit of carnitine is not clearly known. The effect is suggested multifaceted, suppressing toxicity of accumulating Co-A and acyl-carnitine, attenuating generation of ROS, stemming inflammation, and blunting effects of hypoxia and ventricular impairment. Other observations are less apoptosis and necrosis of myocardial cells and normalization in myocardium electrical activity, which beneficially impacts ventricular function and the risk for arrhythmia.

The amount of carnitine supplementation used in heart disease after an ischemic event varies but is in quantity of grams per day for humans. The form of carnitine used varies and is sometimes a conjugate, acetyl-carnitine or propionyl-carnitine because of greater efficaciousness relative to free carnitine. Some caution has been raised about potential toxicity of excess carnitine. Alimentary microbes can metabolize carnitine to trimethylamine, which when absorbed is further metabolized to trimethylamine N-oxide (TMNO). Association of circulating TMNO and heart disease has recently been reported for dogs. A similar caution has not been recognized for taurine. As much as 10 grams of taurine per day are tolerated by humans.

Carnitine in Skeletal Muscle

A high concentration in muscle and knowledge of importance of carnitine in energy metabolism have led to study of exercise performance benefits of supraphysiologic amounts of carnitine in healthy humans. These works in the past have variably shown a performance benefit. More recently, a remedial benefit is appreciated. Extraordinary carnitine intake appears to facilitate recovery of muscle after intense exercise by reducing the extent of exercise-induced hypoxia and muscle injury. Mechanisms are speculative and include recovery of blood flow through support of endothelial function and mitigation of oxidant...
damage from decoupling of cellular energy consumption from energy production.11

Results of a few studies are reported on effects of carnitine supplementation in states of muscle loss in disease of humans. Conditions of interest are inflammatory disease, malignancy, chronic kidney disease, and chronic liver disease.6,7 A few observations indicating mitigation of age-associated sarcopenia are reported for humans. These are particularly relevant to cats, which are living increasingly longer and experience loss of lean mass with advanced age. The means by which carnitine may counter sarcopenia are only suggested. Muscle carnitine of aged humans declines for an uncertain cause. Impaired carnitine homeostasis is suggested. Studies of athletes and animal models indicate supplemental carnitine spares amino acids for protein synthesis by stimulation of fat metabolism and suppression of ubiquitin-mediated protein degeneration. Alleviation of oxidative stress by carnitine may slow putative roles of generated ROS underlying processes of aging.

References


Notes
Abstract

The objective of this work was to study the effect of food texture on feeding behavior and associated food intake in cats. Raw meat from beef carcasses was fed as strips or in puréed form to eight cats, and the number of bites, bite size, oral processing time, and number of meals were recorded. The physical structure of the food had a significant effect on the feeding behavior in cats, but less effect on the amount of food ingested. The study is now continuing to look at beef offal with different textural and palatability properties.

Introduction

Aspects of the feeding behavior of domestic cats remain strongly influenced by their evolutionary history.1 The closest wild ancestor of the domestic cat (Felis silvestris catus) is the African wildcat (F. s. lybica),2 which is a highly specialized predator. As solitary hunters, they kill prey much smaller than themselves, so they require multiple kills to meet their daily nutrient requirements. The domestic cat has retained a similar daily pattern of food intake when fed ad libitum with up to 16 small meals consumed per day.3,4

Domestication of cats occurred relatively late compared to other major domestic species,5 such as the dog. As a result, the domestic cat is relatively less modified from its wild ancestors and has retained the ability to hunt effectively.1 The carnivorous nature is also clearly seen in their dentition,6 with large canines used to kill and hold prey, and premolars and molars for cutting and shearing. Both the chemical and physical characteristics of food regulate intake in cats. Studies have investigated the influence of a food’s chemical composition on intake,7,8 but little work has considered the importance of physical food characteristics. A brain stem central pattern generator9 generates the rhythm of mastication, but its output is modulated by the properties of food being processed, including the size, hardness, and texture of the pieces and the age of the individual.10-15 Research in humans suggests that foods that are consumed quickly and easily cause limited perceived satiation and satiety, which in turn can increase food intake,16 Increasing oral processing time (the time that the food actually is in the mouth) and adjusting several other factors, such as bite size, number of chews, and rate of eating,16 all considered as the “microstructure of feeding,” can have an influence on this and may alter food intake. Although little data exists on oral processing time, data on bite size, number of chews, and rate of eating are available for cats consuming dry (kibble) or wet retorted foods that show relatively little chewing activity.14 These diets are prepared using a batch system and blends of raw ingredients or meat slurries with reduced particle size and are relatively homogenous.17 Unlike these complete foods, raw meat or offal is a complex matrix consisting of myofibrils and connective tissue.18 Meat structure, however, can be altered through dicing, mincing, or puréeing, which allow investigation of the impact of physical structure of food on the feeding behavior in cats as has been reported here.

Animals, Materials and Methods

Eight female desexed domestic shorthair cats (aged 1 to 8 years [3.54±2.45 y] and weighing 3.00±0.27 kg) with full dentition were selected from the Centre for Feline Nutrition colony (Massey University, New Zealand) for this work. The cats were used in three experiments (Massey University Animal Ethics Committee [MUAEC] Protocol Number 15/96), where they received two test diets of differing structure: strips (structured 1x1x2cm) and purée (non-structured).

Both diets were prepared using the same cut of meat (Biceps femoris) or the flat of the outside round from multiple beef carcasses sourced directly from a meat processor (AFFCO Manawatu, Fielding, New Zealand). The two diets used for each experiment were prepared as a single batch, portioned into daily amounts and stored at -28˚C until used for a trial. The levels of nitrogen (N) (for crude protein), crude fat, ash, dry matter, and gross energy were analyzed for each diet (Table 1) in all three experiments. The daily portion of the...
two diets was defrosted overnight at 4 °C before removal to room temperature (20°C) for a further two hours before feeding. A recording system was developed that utilized a USB camera in front of each cage and was held in place by a mechanical arm that allowed flexibility in adjusting the angle and the distance of view. Then, a personal computer was used to run Lab View software (National Instruments, Austin, Texas) that performed a background subtraction algorithm to each cage simultaneously at 25 to 30 frames per second to detect whether the cat was in close contact with the food. At the same time, the program recorded the real time weight of each bowl and associated each weight reading with its corresponding frame while recording (Figure 1).19

In experiment one, the cats were offered the strips and purée for two hours in a two-bowl palatability test.20 To prevent bias, the position of the bowls containing the two diets were switched each day.20 The first diet selected, first diet completely consumed, rate of intake, and total intake were recorded.

In experiment two, the cats were fed the strips for three days followed by three days of feeding purée. Meat (70 g) was offered in the morning and afternoon (140 g/d in total), and leftovers were weighed after two hours. Feeding behavior was captured by the recording system on day three and day six to quantify residence time of food in the oral cavity of the cat per bite (oral processing).

In experiment three, the cats were divided into two groups, with one fed strips (n=4) and the other purée (n=4) for three days. Structure of meat offered to each group was then switched after day three. Meat (385 g, ad libitum) was offered in the morning, and leftovers were weighed after eight hours. Food intake patterns were recorded using the recording system, with mealtime criterion set at 80 s. Data were analyzed using the GLM procedure in SAS with the factor meat structure (strips, purée) included in the MODEL statement. For experiment two, period was also included as a factor in the statistical model.

**Results and Discussion**

Experiment one showed no difference (P>0.05) in intake between the meat strips (45.9±0.7 g) and purée (45.1±1.7 g), indicating both diets were equally palatable. The cats chose the purée first, 52.5% of the time (21/40 observations), and finished the purée first 50% of the time (20/40). This indicated minimal selectivity at the macro level between the two meat structures offered.

Experiment two also showed no difference (P>0.05) in intake between the meat strips (68.8±6.5 g) and purée (66.0±0.1 g), further confirming that both diets were equally palatable. However, close observation of feeding behavior showed the cats consumed the two types of meat differently. The purée was consumed with more bites (38.1 versus 23.4: P=0.017) and remained in the mouth for a longer period than the strips (in total 191.0 versus 74.9 sec: P<0.001). This implies that the bite sizes were smaller for purée than for strips (1.84 versus 2.99 g/bite). In humans, increasing the number of chews, reducing bite size, and reducing eating rate resulted in a reduced *ad libitum* food intake and improved satiety responses.21 Long-term intervention studies reported that slowing down the eating rate beneficially altered the physiological responses to food22 and may be a useful therapy for reducing obesity.22 To investigate if these effects occurred in cats, a longer duration study aimed at capturing meal frequency data was carried out in experiment three.

In experiment three, intake of the strips and purée were again not different (248.2 versus 221.8 g: P>0.05), and large inter-cat variation did not allow a difference in intake patterns between diet structures. However, relative to the strips, the purée was consumed in a numerically greater number of meals (20.1 versus 13.6: P>0.05), with a consequently smaller meal interval (35.1 versus 50.1 sec: P>0.05) and smaller meal size (42.7 versus 18.9g: P>0.05).

These data suggest that although the rate of consumption was slower for the purée diet versus the strips, no reduction in *ad libitum* food intake was observed. Although large inter-cat variation in meal pattern was observed, it is interesting that...
the underlying food intake rhythm in cats consuming each of the foods was close to that reported in the literature despite the differences in rate of consumption of each meal. Future research should be aimed at reproducing these differences in rate of consumption using complete and balanced diets so that longer-term studies can overcome the inherent variation present between animals. The ultimate aim would be to identify textural and structural factors that may interact with bite size, chewing, and eating rate to influence food intake in the long term for the precision feeding of cats. This use of structure and texture may be a useful low-impact mechanism to tailor diets to alleviate obesity issues in pets or alternatively cater for geriatric pets where a decline in nutrient absorptive capacity has been reported.23

Conclusion
The physical structure of the food has a marked effect on the feeding behavior (number of bites, bite size, oral processing time, and number of meals) in cats, but less effect on the amount of food ingested.

References
1. Bradshaw JWS. The Evolutionary Basis for the Feeding Behavior of Domestic Dogs (Canis familiaris) and Cats (Felis catus). J Nutr. 2006;136:1927S-1931S.


Notes
Control of Water Balance

Water is the most plentiful substance in the body, and the maintenance of volume and osmolarity of body compartments is essential for homeostasis. Changes in the extracellular fluid (ECF) alter cell volume, intracellular ionic strength, and pH, and large changes in ECF osmolality can affect the structure and function of macromolecules and ultimately the physical integrity of cells and tissues. More subtle changes in neuronal electrocyte concentrations can affect neuronal excitability and lead to altered mentation. Mammals maintain ECF at around 300 mosmol/kg. Changes in plasma osmolality, and hence interstitial fluid osmolality, are detected as a result of cell shrinkage in the organum vasculosum of the lamina terminalis (OVLT), a circumventricular organ located outside the blood-brain barrier in the anteroventral part of the third ventricle.1

Specialized neurons in the OVLT experience architectural changes in response to ECF osmolality shifts and alter their rate of spontaneous firing. Osmosensitive neurons have projections into the pharyngeal and intestinal mucosae and the hepatic veins.1 These neurons can sense the osmolality of ingested substances before plasma osmolality changes, leading to preemptive drinking. These sensory afferents ascend to the CNS via the vagus. Thus, the magnitude and polarity of the ECF shift results in central and peripheral neural impulses conducted to the hypothalamus, posterior pituitary, and the cortex, controlling thirst, drinking, and antidiuretic hormone (ADH) release. The main renal effect of ADH is to increase the expression of aquaporins in the collecting ducts and allow diffusion of water from the filtrate into the hypertonic medullary interstitium. However, ADH also causes efferent arteriolar constriction and is more potent than noradrenalin at doing so.2 The result of ADH secretion is an increase in GFR and a reduction in papillary blood flow.3

Thirst is stimulated directly by OVLT sensing of increased ECF osmolality and indirectly by ADH release. However, the direct central nervous system (CNS) stimulation by intracarotid infusions is less sensitive to dehydration than the ADH response, so increases in urine concentration in response to an increase in osmolality can occur in the absence of the sensation of thirst. Likewise, during rehydration, thirst disappears before normalization of water balance.4,5 In dehydrated dogs, drinking rapidly inhibits ADH secretion long before any reduction in ECF osmolarity, which is mediated via oropharyngeal osmoreceptors.3 Thus, normalization of plasma osmolarity is slower than might otherwise be the case and may be prolonged if renal concentration capacity is limited. However, although normalization may be delayed, the onset of thirst is still very rapid and may even precede the ADH release following ingestion of a meal. Food ingestion increases plasma osmolarity, and in humans, thirst is stimulated once plasma osmolarity increases from 280 to above 295 mosmol/kg.6

As humans and rodents age, the thirst drive is less sensitive, and satiety is achieved at greater deviations from normal osmolarity than in younger individuals.7,8 It is not yet known if this is due to decreased sensitivity of central osmoreceptors or a reduced response of higher cortical centres to signalling from the OVLT.7 This makes geriatric people more susceptible to dehydration.10-11 Although the exact mechanisms are not precisely determined, it is not due to reduced ADH secretion.10,12 As such, the combination of increased risk of dehydration and appropriate ADH release in response increases the exposure of the kidneys to ADH effects in the elderly. However, it is not known if these age-dependent changes are also present in cats or dogs. Until proven otherwise, it is reasonable to assume they are.

Factors that combine to decreased fluid intake in geriatric animals include decreased renal tubular concentration capacity, decreased mobility, and dementia. Subclinical dehydration impairs cognitive performance and memory and depresses mood in humans, and is likely to have similar effects in dogs and cats.13 Thus, some of the depressed mentation associated with age may be related to suboptimal hydration. When cats are acutely switched from wet to dry diets, we have observed both delayed increase in voluntary water intake and a reduced maximal response in older cats compared with younger cats (Figure 1). This suggests that they, too, may have an increased risk of dehydration as they age.

Veterinary texts have long repeated the general clinical features that indicate the degree of dehydration. Although these are widely accepted criteria, the accuracy of physical

Abbreviations
ADH: Antidiuretic Hormone
CHF: Congestive Heart Failure
CKD: Chronic Kidney Disease
CNS: Central Nervous System
ECF: Extracellular Fluid
HPDs: Home-Prepared Diets
OVLT: Organum Vasculosum of the Lamina Terminalis
UPC: Urine Protein-to-Creatinine Ratio
USG: Urine Specific Gravity

Dry Matter, Wet Matter, Does It Matter?

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signs to estimate the degree of dehydration has been called into question. In a study of almost 200 dogs and cats presenting to a veterinary teaching hospital, the criteria were tested against the standard of increase in body weight following intravenous fluid therapy. In that study, it was shown that application of the criteria is highly inaccurate regardless of the expertise of the attending clinician. Thus, a clinical suspicion based on a combination of history and physical examination findings and a presumption of dehydration until proven otherwise may be as sensible as the continued use of an inaccurate, if beloved, scale.

Water requirements are frequently expressed as 40-60 mL/kg/24 hours. However, the true water requirements are better expressed relative to the amount of food consumed, and hence energy expenditure. Under laboratory or hospital settings, dogs and cats will naturally consume a total (voluntary plus dietary intake) 0.1-0.2 mL:kJ. At dietary moisture contents of >75%, even with very high fat contents, both cats and dogs will usually obtain sufficient dietary water to meet their requirements, and voluntary intake will cease. Thus, owners switching pets from moist to dry diets may be surprised by the associated increase in voluntary intake.

Meal feeding results in lower total water intake than when cats are fed ad libitum. In addition, we have shown that cats allowed dry food (5% moisture) ad libitum will consume their daily requirement much quicker than when offered wet food (>75% moisture) ad libitum. In response, cats will gradually drink their water requirement over the course of the day when fed dry food and thus will spend the majority of the 24-hour period in a state of subclinical dehydration.

Dietary moisture has been suggested as a possible means by which the energy density can be decreased, and total energy intake decreased. Although water has a low or insignificant effect on food satiety in most mammals, food intake could be altered due to non-satiating effects. When cats were meal-fed diets (bid) that differed only in their water content, voluntary intake and body fat mass was greater in cats fed a 10% moisture diet than an 80% moisture diet. In another study, where cats were forced to lose weight during energy restriction, they regained less when offered 52% moisture food ad libitum than they did when offered 12% moisture food ad libitum. The effect of increasing dietary moisture on body weight could be solely to decrease voluntary food intake, or it could also increase energy expenditure. Total daily activity has been shown to be higher in cats fed high-moisture diets compared to low-moisture diets, though to date a study of total energy expenditure has not been made.

Thus, high-moisture food may reduce voluntary intake, reduce rebound following planned weight loss, and be associated with increased activity and probably energy expenditure. However, although the magnitude of this effect has not been studied in home settings, it is unlikely to be great since epidemiological studies conflict on the importance of dry food as a risk factor for obesity. In several studies, neither canned diets nor moist home-prepared diets (HPDs) has been associated with a decreased prevalence of obesity.

Wet Versus Dry Food

Both cats and dogs adjust their drinking in response to changes in dietary moisture. Studies of the accuracy of this response have either evaluated a small number of dietary moistures or used diets of different macronutrient composition. We have evaluated the total and voluntary intake of
cats when fed the same diet but with varying water content, from 5 to 85% moisture (Figure 2). Between 65 and 5% moisture, cats adequately adjust voluntary intake such that the total water intake remains constant. At 75%, they stop drinking, and at 85%, total intake increases and diuresis results. Between 65 and 5%, urine specific gravity (USG) remains near maximal and relatively constant. Thus, to reliably reduce urine concentration, at least 75% dietary moisture needs to be fed, and simply “adding some wet food” to a dry food diet is unlikely to have a significant effect on USG. This may explain why some studies have not shown a beneficial effect to wet diet feeding. For reducing USG, an effect may only be seen with sole feeding of a wet diet.

It is important to realize that although the total water intake may be equal, animals on dry diets are in a different physiological state than animals on wet diets. If the daily dry matter intake is consumed in a short space of time, the animal will be in a state of mild dehydration (hypohydration) until the drinking has “caught up” with the water deficit. During that time, ADH secretion will be increased, and consequently glomerular filtration pressure will be elevated relative to an animal fed a wet diet. We have shown that normal healthy cats consuming a 5% moisture diet with ad libitum access to food have an increased urine protein-to-creatinine (UPC) ratio than when consuming 45% or 85% moisture diets (Figure 3).

Although the amount of proteinuria is not “pathological,” one is forced to ask if it could be deleterious in the long term. To put it in perspective, it has recently been shown that the UPC is an independent risk factor for the progression of chronic kidney disease (CKD) in cats.18 In that study, cats with CKD that progressed during the study period had a UPC significantly greater than cats with stable CKD. When the UPC of the cats is graphed against the healthy cats, it supports the hypothesis that dry diets are probably inferior in the long-term management of CKD.

Renal Hyperplasia

The kidney adapts to changes in solute delivery and water intake. Minute-by-minute variations in blood flow, GFR, GRP, sodium, and water resorption can produce changes in urine volume and osmolarity with speed. Chronic changes in water intake, however, can produce structural adaptations. In rodents, chronic increases in ADH secretion lead to renal medullary enlargement, predominantly due to hypertrophy of the thick ascending limb of the loop of Henle.9 This has been shown to be specific to cells expressing the V2 ADH receptor.20 In cats maintained for years on dry diets, the ratio of cortex:medulla was significantly different to those maintained on wet diets (unpublished observation). Whether the changes seen in cats are simply the response to chronic ADH differences or due to other dietary differences is unknown, as is the functional or clinical significance.

Water Intake in Disease

Water is integral to the management of lower urinary tract diseases. The single most important intervention for urolithiasis and idiopathic cystitis is to reduce the urine osmolarity. Increasing dietary water intake can significantly reduce the proportion of cats with idiopathic cystitis that experience recurrence of clinical signs. Clinical signs of recurrent idiopathic cystitis was seen in 11% of cats that were fed a canned diet compared with 39% of cats fed a similar dry diet designed to result in production of an acidic urine.21 Attempts to increase drinking by providing a source of running water has not yet proven to be effective. In one study of nine household cats, there was no significant effect of water intake when cats were offered water in a fountain compared with a bowl.22 In another study, although water intake from the fountain was slightly greater, the cats’ USG was no different and remained very high.23 All cats were fed dry diets. A similar study in dogs has not yet been published.

In rats with surgically created CKD, an increase in dietary moisture reduces plasma ADH and urinary osmolarity.24 Surprisingly, CKD progressed much slower, and there was dramatically reduced urinary protein excretion, reduced hypertension, kidney hypertrophy, and incidence of glomerulosclerosis, and mortality. Antagonism of ADH reduces proteinuria, reduces glomerulosclerosis, and has an added benefit to ACE-inhibition in surgically induced CKD in rats.25 Thus, it appears that ADH has an independent role in the progression of CKD related to the effect of ADH on glomerular filtration pressure and proteinuria. What needs to be established is the clinical importance of reducing ADH by maximizing water intake.
The restriction of dietary sodium has long been considered an integral component of the management of congestive heart failure (CHF) in dogs. In one of the few studies to directly evaluate the effects of dietary sodium restriction in 14 dogs with CHF, most echocardiographic indices improved, but plasma aldosterone, atrial natriuretic peptide, and renin were not affected. Plasma ADH was not measured in that study. However, ADH antagonism in dogs with CHF has been shown to decrease pulmonary capillary wedge pressure but had no effect on GFR, renal blood flow, or systemic arterial blood pressure. Cats fed dry food develop less calculus and gingivitis than cats exclusively fed canned food. In a large survey of domestic cats in Japan, calculus was more common in cats fed canned or home-cooked meals than cats fed dry foods (41% versus 25%). Similarly, it was shown many years ago that soaking dry food prior to feeding is a reliable method of inducing the rapid formation of plaque, calculus, gingivitis, and eventually periodontitis in dogs. In a large study of several thousand dogs and cats in Poland, animals fed high-moisture HPDs had significantly poorer oral health than animals fed commercial canned food, which was worse than animals fed dry food. This is consistent with the abrasive and reduced deposition effect of harder food. However, the difference between high-moisture HPDs and commercial canned food also illustrates that there are factors other than physical effects that influence oral health.

Conclusion
Water is an essential element that is infrequently considered in nutritional studies. The management of several important and common diseases includes attempts to reduce urine concentration. The most reliable method for achieving that goal is to increase dietary moisture content, but it needs to be more than 65% moisture. Both diseased and healthy animals are not physiologically identical when consuming dry and wet diets, even with an equal daily total water intake, and there may be a cost to the chronic increased ADH secretion. Studies are sorely needed that address the independent role of dietary moisture on several diseases, most notably CKD. Remaining questions include whether dry diets increase the risk of CKD, accelerate the progression of CKD once established, and increase the risk of dehydration in older cats, and whether increases in dietary moisture could be used to reduce the risk of obesity.

References


Cats Reorganize Their Feeding Behaviors Following A Mild Calorie Restriction

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Abstract
Obesity and its associated health issues are a major concern in the worldwide cat population.1-4 Calorie restriction is commonly prescribed as part of the dietary management for addressing and/or preventing feline obesity. However, very little scientific information is published about how calorie restriction affects the feeding behavior of cats. Here, we provide a brief summary from a study to evaluate cats’ feeding behavior when they are no longer allowed ad libitum access to food.

Introduction
When domestic pet cats are offered ad libitum access to food, it increases their risk for obesity.5-9 The percentage of overweight or obese cats was recently estimated between 22 and 52% depending on studies and countries,7,10-13 and even reached 60% in the U.S. in 2017.14 Consequently, veterinarians often recommend calorie restriction as a strategy for preventing or addressing feline obesity.15 From cats’ perspective, calorie restriction not only results in less calories available for ingestion, but also they no longer have control over some aspects of food availability and how much to eat. Prey availability and value were seen to greatly influence meal size and frequency in lions in the Serengeti National Park.16 Research has also shown that as the effort or cost to obtain food increased, domestic cats would alter their meal patterns in significant ways.17,18 Thus, it is expected that even with a mild calorie restriction, domestic cats will reorganize their feeding behavior differently than when fed ad libitum.

Effects of Calorie Cutoff on the Weight and Feeding Behavior of Cats
In the present work, we studied two groups of cats: a control group (N=31; age: 7.5±4.1 years; weight: 4.4±0.8 kg; BCS: 5.7±0.8; 58% of BCS>5) and a test group (N=38; age: 8.3±4.0 years; weight: 4.2±0.9 kg; BCS: 5.3±0.8; 34% of BCS>5). The control group had ad libitum access to food over the 11-month study, while the test group was initially fed ad libitum one month, then underwent nine months of mild calorie restriction (i.e., average 6% of their maintenance energy requirement [MER]) before being allowed back to ad libitum food access during the last month of the study.

The non-overweight cats of the test group were not restricted but limited to the calories needed to keep them at their current weight. Both groups received the same variety of wet and dry standard commercial maintenance foods according to the same schedule over the entire study. The body weight of cats was measured monthly during the first 10 months and weekly during the last month of the study. Assessments of the feeding behaviors for both groups were taking place during reference test periods at T0 (ad libitum), T+9 months (restriction for the experimental group only), and T+10 months (ad libitum) when cats were submitted to the same feeding plan including both wet and dry foods.

The overweight cats of the test group significantly lost weight during the calorie-restriction period (p<0.01). However, once those cats were allowed back to ad libitum food access, their weight increased back to their initial level. Calorie restriction affected the feeding patterns of the cats of the test group with changes observed besides others in several temporal parameters, meal frequency, and size (Table 1). Further details will be shared during the presentation.

Conclusions
Results supported that calorie restriction is an effective strategy to control cats’ weight. In addition, as hypothesized, cats reorganized their feeding behavior when submitted to a mild calorie restriction compared to when fed ad libitum.

Table 1. Evolution of some feeding pattern parameters of the control and test groups between T0 when no restriction was at play for any group and at the end of the calorie cutoff period for the test group (T+9 mo.). Blue arrow = significant evolution (p<0.05); black arrow = statistical trend or significant evolution depending on food type (p≤0.1); ns = no significant evolution (p>0.1).

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<td>Consumption Per Meal (g)</td>
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Abbreviations
BCS: Body Condition Score
MER: Maintenance Energy Requirement

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they were fed *ad libitum*. Those changes may account for some of the difficulties to get cat owners’ commitment to weight-loss programs. The present data also indicated that nutritional strategies that rely less on calorie restriction are of major importance for cat weight management. If calorie restriction is to be used, feeding strategies should be leveraged to help cats maintain normal feeding patterns.

**References**


Can Pet Health Technology Improve Outcomes In A Multi-Cat Household Weight Management Program While Preserving The Human-Animal Bond?

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Abstract
With the feline overweight and obesity rate now over 60%, practicing veterinarians need a better understanding of feline feeding behavior and as many tools as possible to be successful in feline weight-management programs, especially in multiple-cat households. Pets Reducing for Rescues partnered with the Ontario Veterinary College to conduct a feline weight-management pilot study using a home health technology ecosystem consisting of an electronic scale, smart feeder, an activity monitor, and a webcam/treat dispenser. We found favorable weight-loss rates, a lower dropout rate, and cat and pet owner acceptance of home health technology while respecting and keeping the human animal bond intact.

Up to 60% of cats are now overweight or obese (Association for Pet Obesity Prevention [APOP] Survey, 2017), and two sources report it is still increasing (APOP, 2017, and Banfield, 2017). The Global Pet Obesity Initiative Position Statement that has been approved by over 23 veterinary organizations now classifies pet obesity as a disease. Obesity has been shown to be a significant risk factor, predisposing cats to diabetes mellitus, orthopedic disease, neoplasia, urinary problems, and skin conditions. The recent publication of the American Association of Feline Practitioners (AAFP) Consensus Statement on Feline Feeding Programs outlines the important areas that need to be addressed to feed cats in a healthy way to avoid stress and undesirable outcomes, one of which is obesity. It is time for practitioners to enhance the educational tools and dialogues we use to help solve the obesity epidemic in cats.

The practicing veterinarian is in a challenging position to implement feline weight-management programs (WMPs). Pet food sales are increasingly online with a myriad of consumer choices, many with high-caloric density and varying protein levels. In addition, consumers often opt for automatic feeders and use consumer-facing apps and pet products that recommend certain foods without any valid basis. It takes considerable time to dialogue with clients and sort through the many (sometimes emotional) food ingredient choices with the goal of steering them toward a purpose-formulated food if the pet's body condition score (BCS) is 7-9/9. This dialogue must be delicately handled, and the human-animal bond (HAB) respected to avoid alienation of the client.

There are inherent risks with caloric restriction in obese cats including hepatic lipidosis and muscle wasting. Cat behaviors are challenging for clients to deal with, and at least a basic understanding of the cat’s environmental needs in the home must exist for the cat’s well-being.

With the average cat household in the U.S. having 2.1 cats (American Veterinary Medical Association [AVMA] U.S. Pet Owner Sourcebook, 2012), additional challenges arise, in particular the need for multiple resources, food stealing, and inter-cat behaviors.

Clearly, feline obesity treatment and prevention is a perfect storm of making food recommendations amid “food option chaos,” lack of education regarding cat feeding behaviors, and the challenges of caloric restriction in the cat. When creating a WMP, all of these issues need to be addressed with veterinary supervision during limited clinic visits that the cat (and client) are sometimes reluctant to make due to travel. How can we as practicing veterinarians successfully leverage emerging technology to help solve this challenge while respecting the amazing species that is Felis catus?

Reason for Pilot Study
The target for weight loss in cats in a WMP is generally 1 to 2% per week from the initial weight. Studies in home
WMPs in cats are relatively scarce compared to dogs.\textsuperscript{5,10-16} Two recent large multicentric studies in pet cats, each using a purpose-formulated, weight-management food, showed weight loss of 0.45% over six months and 0.8% over 12 weeks.\textsuperscript{3,11} Previous home studies showed weekly body weight (BW) losses of 0.5 to 0.8\% for cats\textsuperscript{13-18} and 0.9\% for dogs.\textsuperscript{16} In colony cats, 1.2 to 2\% has been reported.\textsuperscript{17,20} Dropout rates in home WMPs have been reported at 39\% in dogs\textsuperscript{16} and 41\% in cats in a 12-week study with 86\% of the dropouts due to lack of clinic follow-ups.\textsuperscript{19}

The lower rates of weight loss demonstrated in home studies versus colony cats are likely due to the many challenges of clients in a home environment, particularly the: 1) clarity of veterinary recommendation, 2) accuracy in measuring and delivering food, 3) need for interim metrics, especially BW, 4) effect of cat behaviors during caloric restriction on owners’ compliance,\textsuperscript{21} and 5) exercise. These five major challenges led us to hypothesize that emerging technology could help improve the rate of weight loss, reduce the dropout rate while positively affecting perceived cat happiness, and increase client satisfaction during a WMP in a multiple-cat household.

**Pilot Study Abstract**

Pets Reducing for Rescues partnered with the Ontario Veterinary College in Guelph in a pilot study in the fourth-quarter of 2018 with the objective of establishing how a Pet Health Technology Ecosystem (PHTE), consisting of a smart feeder, webcam, activity monitor/app, and digital scale, could be used in a WMP in multiple-cat households (Figure 1). Eight veterinarians supervised households of two indoor-only cats in which at least one cat had a BCS of 7-9/9. The veterinarians were first instructed to perform a nutritional assessment and calorie calculations using the Pet Nutrition Alliance calculator (0.8xRER), with an initial goal of 1\% body weight loss per week with two-week check-ins. A two-week period of technology/diet acclimation was followed by four weeks of caloric restriction. Clients were instructed to weigh cats twice weekly and enter those weights in both a paper diary and an activity monitor app, along with any observations regarding cat behavior or device issues, including webcam video clips. Research ethics board approval and participant consent were obtained to administer a survey to clients and veterinarians afterward to collect their observations of cat behaviors, satisfaction with the various devices, and measure the human-animal bond. Four of nine owner and eight of nine veterinary surveys were returned. Diaries from eight of nine owners were returned. Average weight loss was 0.85\% over a four-week period for the 14 cats. Dropout rate was 22\%.

A PHTE was found to be effective for gathering weight-management data remotely, and this short, small, uncontrolled pilot study resulted in weight-loss rates similar to what has been previously reported without a strict feeding protocol. A randomized controlled study for further investigation is planned in 2019. Co-authors of the pilot study are Barr Hadar, DVM, PhD, a post-doctorate student in epidemiology at the Ontario Veterinary College (2018-2022), and Theresa Bernardo, DVM, MSc, professor of epidemiology at the Ontario Veterinary College and IDEXX chair in emerging technologies and bond-centered animal healthcare.

**Discussion**

The major findings of our pilot study were that in order for technology to help in a WMP in a multiple-cat household, there needs to be a clear step-by-step implementation, starting with the nutritional assessment, food choice, and caloric restriction guidance from the veterinarian, and regular reassessments with a clear respect for both human and pet behaviors. These are clearly outlined in the American Animal Hospital Association (AAHA) Weight Management Guidelines,\textsuperscript{9} with the authors eloquently stating: “Weight loss is achieved with appropriate caloric restriction, diet selection, exercise, and strategies to help modify the behavior of both the pet and client. The success of any program depends on partnering with clients to set expectations, promote client compliance and treatment adherence (compliance and adherence describe the degree to which the client correctly implements medical advice and continues an agreed-on mode of treatment), and overcome challenges presented by each pet.”

Self-assessment including diaries has been shown to be consistently helpful in weight-loss programs in people.\textsuperscript{22} The handwritten diary used in our pilot study was found to be a valuable resource to follow BW metrics, behaviors, and device malfunctions (Figure 2). The survey provided insight to the issues of feeding cats using technology (Tables 1-3 and
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5. It became clear that for a WMP to succeed, especially in multiple-cat households, lots of data and education are needed to see where the cat’s needs and behaviors intersect with human needs and behavior.

The Challenges of a WMP for Cats
To be successful, the veterinarian/veterinary team must overcome these challenges:
1) Conduct a complete nutritional assessment with appropriate metrics (BW, MCS, BCS) for any cat in practice
2) Get client buy-in and participation via dialogue
3) Choose a prescription food for cats with a BCS greater than 7/9 and help them choose an over-the-counter food for cats with a BCS of 5-6/9
4) Calculate amount to feed using PNA calculator (0.8xRER) as starting point and send PNA calculations and diary sheet home with client
5) Get client/cat back for physical reassessments and regular telehealth “visits” (phone, text, video chat, email)
The clients of overweight or obese cats face these challenges after they elect to embark on a WMP:
1) Allocating the correct amount for each cat and preventing food stealing
2) Feeding cat in as natural a way as possible (six to eight times a day, separate food stations out of sight of one other, simulate hunt and forage)
3) Deal with cat behavior issues related to caloric restriction (begging, vocalization, inter-cat aggression, etc.)
4) Reassessing metrics (BW) at home

The challenges ranked as most common from surveys for both clients and veterinarians from the pilot study are listed in Table 4.

**Cat Need #1: Multiple Food & Water Stations**
Cats are solitary predators that consume small prey, and they prefer to eat often and alone out of sight of other cats.23 In a multiple-cat household that means we have to provide a separate feeding station for each cat in order to prevent stress.

**Cat Need #2: Frequent Small Portions Per Day**
Cats in the wild eat several times per day. Their prey is typically a lower-caloric density than today’s commercial diets, so they would have to hunt and kill up to six to eight times per day necessitating many kills per day — and many missed attempts — to meet their basic nutritional requirement. Considerable energy is expended in these efforts,24 which would not occur in a home environment unless hunting is simulated.

**Cat Need #3: Ability to Hunt & Forage/Exercise**
Outdoor cats typically spend over 50% of their time hunting.25 The cat’s natural instincts and intelligent, inquisitive nature must be respected and activity provided for if confined indoors. Puzzle feeders are a wonderful step forward.26 Their use in multiple-cat households is a challenge as the owners need to be willing and able to spend the time required making sure the daily allocation of food accomplishes the caloric restriction prescribed for each cat in the household. At least one pilot study showed puzzle feeding did not increase cat activity as measured by accelerometry.27 Additional studies and solutions are needed.

**Meeting Specific Challenges While Using Smart-Connected Technology and Meeting Cats Feeding Needs**

**Challenge #1: Delivering the Correct Amount of Food Multiple Times Per Day to the Correct Cat**

**Technology Solution:** Smart Feeder
There are many automatic feeders on the market, but few will accurately deliver a prescribed amount in a cat-friendly, cat-controlled manner. There are two primary criteria for smart feeders.

A) **Timed/Portion Control (How Many Times Per Day/ How Much)** There are many feeders available in which owners can control the amount to be fed per day and how many times per day either directly on the device or using an app. The two key criteria for weight-management and obesity prevention are: 1) Can they portion control six to eight times per day, and 2) Can they accurately deliver amounts as low as 5/16 to 3/8 cup (equal to 5 to 6 tablespoons) per day, as cats with ideal weight goal of 8 pounds will only need that amount if fed a food around 300 cal/cup.

B) **Cat Controlled (Which Cat Can Eat from Which Feeder)**
These feeders can control which cat is allowed to eat by using a microchip, RFID or microchip tag. Surefeed and PortionProRx are examples. Facial recognition is being explored that would not require a collar/tag or microchip. Other considerations include:

C) **Accuracy**
The measuring problem: Even 10 calories/day per day extra (about 10 kibbles of typical dry cat food) is equal 1 pound of adipose tissue in one year.28 Using a gram scale to weigh per portion or per day is ideal.28

D) **Wet Versus Dry**
Currently there are no cat-controlled feeders that time/portion control and also feed canned food. It would truly be a major step forward as many feline practitioners would prefer wet food for weight management, and for some cat diseases (urinary), wet food feeding is preferred by most. There is one study that indicates that dry food feeding may predispose to obesity,29 but several that do not.30,31 There are not currently enough studies to ascertain if dry or wet feeding is more effective for WMPs.

E) **Cat Friendly**
Getting the cat used to the new feeder at its feeding station is very important. All of these feeders make some noise when opening/closing, and introduction should be gradual. Interestingly, some cats are activated by the noise of the feeder and come running at the slightest noise simulating a brief “hunt.” They can also become inadvertent puzzle feeders, as cats can smell the food and clearly know they may open at some point and often work to make that happen sooner. In our experience with the Pets Reducing for Rescues contest and programs and our recent pilot study, unless the client is able to feed multiple cats separately at least three times a day by physical separation or use of microchip-activated doors for rooms or feeding chambers, a feeder that meets criteria from A) to E) would provide the ideal solution to work in multiple-cat households during a WMP. Their inclusion in a PHTE for a WMP was highly rated by both veterinarians and clients (see Table 1).

**Challenge #2: Reassessment of BW**

**Technology Solution:** Digital Home Scale and Emerging Smart Scales

Getting the cat reweighed/reassessed is a major challenge in a WMP. If even a small portion of the 86% of WMP dropouts referenced earlier related to a lack of follow-up visits could be retained by “home metric engagement,” it would likely help reduce those numbers considerably.

Electronic baby scales accurate to around 0.02 pound are now available for less than $50. Placing the scale near the...
cats’ favorite sleeping area with their favorite bed or blanket, a treat on the scale can drastically improve obtaining interim BWs. Due to the cat’s independent nature, obtaining a passive BW would be ideal. This would not only be a benefit in a WMP but also in obesity prevention in young cats and help to detect the many diseases that cause weight loss (renal disease, diabetes, neoplasia, etc.).

The first passive smart scale with app (Toletta) is expected on the U.S. market in mid-2019. It is a facial recognition litter box with built-in scale that will send weights to an app with every litter box visit allowing passive body weights and visit frequency, which would be invaluable for weight management and detection of weight loss or litter box visit irregularities. The placement of a smart scale in front of food or water bowls would be another passive weight capture setup. Digital home scales were strongly appreciated by both veterinarians and clients for use in our pilot WMP study (Table 2).

**Challenge #3:** Keeping Track of Metrics/Use of an Online Diary

**Technology Solution:** Diary on the App that Comes with Fitness Device, Feeder or Scale to Share Data with the Veterinarian

As previously mentioned, we found diaries engaged clients and encouraged the collection of data important to the success of a WMP. It would be a huge timesaver to have an online diary that is easily shared to improve veterinary supervision and allow intervention. We used the BabelBark platform in our recent pilot study, and participants were able to log weights that were then accessible to our clinic’s portal to allow monitoring of trends. We are currently working with other wearables to simplify WMP metric (BW, MCS, BCS) collection as well as amounts and type of food fed, treats, etc., and owner observations. Eight of nine paper diaries were returned and contained valuable observations and data (Figure 1, Table 3).

**Challenge #4:** Monitoring Cat Activity

**Technology Solution:** Cat Activity Monitor

Similar to observing cat behaviors, our lack of “time intersection” with our cats might benefit from a technology assist with regard to objectively documenting cat activity. While the algorithms on pet fitness monitors are not near what they are in people, they are improving and great potential exists. The primary problems in cats have been large size and short battery life. These have been overcome with the next generation (BabelBark and FitBark 2), which are quite small and have a six-month battery life. It has been reported that cat activity increased in 49% of cats by owner observation during a weight-management program. It would be ideal if that could be quantitated. The only monitor to date that has been validated in cats is the Actical, which is a research-oriented wearable that is quite expensive.

We hope to show in a future study that the new generation of small cat friendly wearable technology can be useful to document changes in cat activity during a WMP. Further, as collar mounted devices are one of the few practical ways to control devices at a distance and record data, if two or three devices become needed to allow access to a feeder and a scale, cats in multiple-cat households might soon need a universal “feline remote control” of sorts!

**Challenge #5:** Keeping Track of Feeding-Related Behaviors

**Technology Solution:** Motion/Sound Activated Webcams

The combination of cat owners rarely being home and cats sleeping or napping most of every 24-hour period makes observation of the cat’s daily activities difficult. The development of cost-effective, motion-activated “nanny & pet cams” has changed that.

**Inter-Cat Feeding Behavior** If the typical owner is home only eight hours to watch the cat and the cat eats between three and eight times per day, a very narrow intersection of observation time exists. The motion-activated recording of feeding behaviors provided by the Petcube Bites web camera and treat provider was a sound solution to capturing intercat feeding behavior in our pilot study (Table 5). In three video clips, food stealing was captured that explained why the “food thief” was not losing weight. The owner had not properly set up the smart feeder, failing to program the tag to close the feeder for the “intruder cat.”

The educational and diagnostic value of these to monitor food allocation, intercat aggression, and other behavioral issues (house soiling, etc.) in multiple-cat households cannot be overemphasized. There are several webcams on the market that will dispense treats as well as provide webcam surveillance. If dispensed treats can be kept to 10% (or less) of daily caloric needs for each cat, the activity expended could be considered a form of hunting/exercise. This could provide a positive/natural experience for the cat as well as enhance the human-animal bond by providing a positive remote interaction and could be a valuable component of a PHTE.

**Challenge #6:** Increasing Activity

**Technology Solution:** Smart Exercise Devices

Any WMP needs to include an exercise prescription. There are numerous devices that show promise to increase activity. Most of them fall into three categories for cats:

1) A stationary device that uses a laser to stimulate cat activity,
2) A device that moves or has moveable parts to entice cats to chase, or 3) Device flings or drops treats simulating a hunt. Once again, unless these are very high-tech and can automatically exercise cats, time, energy, and commitment from the owner is vital for their success. None has yet achieved the “holy grail” of cat hunt/forage/feeding device, in essence a robotic mouse that dispenses the correct amount of food...
multiple times per day to each cat and at some point leads them to a smart scale!

The Future: What effect will technology have on cat-to-human affection, cat-to-cat interactions, and the human-animal bond as we add more accurate, effective devices?

Cats show more affection in a WMP. Allowing clients to be in control of treat feeding as described and having clients directly feed a portion of daily calories in wet food are ways to keep them involved in the equation. Client comments of PHTE use indicated the human-animal bond was affected in a positive way (Table 4). Further studies are planned and needed.

Choice of Individual Devices & Cost of a PHTE Ecosystem?

Finding the best combination of products for each individual cat household is a project in itself. Cats and cat households are truly unique; one size does not fit all. Additionally, these devices are not inexpensive. A good feeder that delivers accurate, timed portions and is cat-controlled are $140 to $290. Scales are between $50 and $150. Add in a webcam/play device at $30 to $200, a fitness monitor at $30 to $80, and it totals from $250 to $725. Too much to pay? A typical diabetic workup would easily be more that the cost of a top-of-the-line PHTE. More importantly, many of the incalculable costs of osteoarthritis, inflammatory diseases related to obesity, and general loss of vitality could be saved.

Summary

Regarding this species, Felis catus, that fascinates, challenges, and intrigues so many of us on a daily if not a moment-to-moment basis, the idea of putting together a PHTE came from having clients try these devices in our Pets Reducing for Rescues (PRFR) annual healthy weight contest and from housing foster WMP cats in Bug’s Cat Gym, a unique homelike boarding, socialization, and weight-management center. Being able to beta test new products and determine the best fit has been educational, fun, and challenging. Our work as feline WMP educators has just begun. Questions like: 1) What is the difference between affection and food-seeking behavior, hunger, and begging? 2) Will our clients ever accept ALL of normal cat behaviors (hunting, foraging, playing, and yes, scratching) and let them just be cats? We are truly the ones who can best educate clients about the value of healthy weight to the cat’s psychological and physiological well-being and its impact on a lower cost of their health care, while maintaining and strengthening the human-animal bond.

References
14. Szabo J, Ibrahim WH, Sunvold GD. Effect of Dietary Protein Quality and Essential Fatty Acids on Fatty Acid Composition


Notes
Notes
Phosphorus Homeostasis: Multi-Tissue Axis Control By The Gut, Kidneys, Bone, And Hormones

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Introduction
After calcium, phosphorus is the second most prevalent mineral in humans, dogs, and cats and makes up about 1% of total body weight. Like calcium, the highest proportion of phosphorus is in bone (approximately 86% as hydroxyapatite). Phosphorus is found in tissues other than bone, the most prominent being muscle, which accounts for 8.6% of this mineral. Approximately 14% of phosphorus is intracellular, being stored in soft tissues such as muscle and 1% is in the extracellular fluid. The 1% in the extracellular fluid includes circulating inorganic phosphate. Phosphorus is involved in many of the metabolic reactions in the body including energy metabolism, skeletal development and bone integrity, muscle function, lipid metabolism, acid-base and osmotic balance, electrolyte transport, cell signaling, protein synthesis, and it is a component of nucleic acids.

Phosphorus Homeostasis
Phosphorus homeostasis is controlled by a multi-organ axis that includes the gastrointestinal tract, kidneys, parathyroid gland, and bone. Dietary phosphorus is absorbed through the intestine. Bone constitutes the major storage form of phosphorus, and the kidneys filter, reabsorb, and excrete phosphorus from the body. Almost 100% of serum phosphate is filtered by the renal glomerulus, and of that 80 to 90% is reabsorbed by active transporters. The parathyroid gland, bone, and kidney are also endocrine organs that produce the hormones that regulate phosphorus. These hormones are parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23) and its cofactor klotho, and 1,25-dihydroxyvitamin D (1,25(OH)2D). The latter is known as active vitamin D or calcitriol. In healthy animals PTH, 1,25(OH)2D, FGF23 (and klotho) maintain serum phosphate in the normal range by regulating urinary phosphate excretion. In healthy adult animals the amount of phosphate in the urine approximates the amount of phosphorus absorbed by the intestines.

Phosphorus absorption occurs throughout the small intestine. In humans and rats, absorption is greatest in the jejunum, lower in the duodenum, and minimal in the ileum. In the rabbit, phosphorus absorption is maximal in the duodenum and decreases through the length of the small intestine. There is no phosphorus absorbed through the colon of the rat. Intestinal phosphorus absorption occurs similarly to renal phosphate reabsorption in that it contains an active, sodium-dependent component of phosphorus absorption. This is accomplished by a combination of a saturable, carrier-mediated transporter component (sodium dependent) and a non-saturable, concentration-dependent component that is sodium independent and is characterized by paracellular diffusion. The carrier-mediated component in the gastrointestinal tract is in the form of type II and III sodium-dependent phosphorus transporters. Calcitriol has a role in the regulation of intestinal phosphorus absorption by increasing gene expression of the type III transporters (PiT-2), and post-transcriptionally regulating expression of the type II transporter NaPiIIb. The sodium-dependent transporters are up- and downregulated based on the animal’s needs, whereas the sodium-independent component (paracellular diffusion) is influenced by the amount of phosphorus consumed.

Several studies evaluated the regulation of paracellular diffusion of phosphorus by determining the impact of feeding increasing amounts of calcium and phosphorus in healthy cats. Healthy adult cats were fed increasing amounts of calcium and phosphorus in the form of dicalcium phosphate. The calcium-to-phosphorus (Ca:P) ratio was 1:1 to 1.2:1. Apparent absorption of phosphorus ranged from 26 to 42%, however, this range was not correlated with dietary phosphorus. Urinary phosphate increased linearly with dietary phosphorus. Diet had no effect on serum phosphate. Other studies examining the effect of increasing phosphorus (in diets with a reduced Ca:P) on digestion and excretion reported that both increased as the concentration of phosphorus increased in the diet. In one study, apparent digestion of phosphorus increased from 40 to 60% as total dietary phosphorus increased from 0.56 to 1.6% with the addition of inorganic phosphorus. As phosphorus intake increases...
so does intestinal uptake of phosphorus with paracellular diffusion, making it difficult to know if the difference in phosphorus digestion was the result of the source or amount of phosphorus. The role of the reduced Ca:P ratio may have had an influence as well.24,27,28

The apparent digestibility of phosphorus is reported to be between 0 to upward of 80%.7,25,28,32 There are two basic types of phosphorus in food,7 organic (sometimes referred to as natural) and inorganic. Phosphorus from inorganic sources (as in phosphate-containing preservatives) is generally more bioavailable than that from organic sources.33 Phosphorus from plant sources are less bioavailable than both organic and inorganic sources of phosphorus due to binding with phytates (salts of hexaphosphorylated inositol).13 Digestibility of such sources is reported to be between 0 to 40%.7,15,28,32 Inorganic phosphorus, as found in phosphate-containing preservatives, is reported to have an uptake of 80% or more.7,15,32

In one study, cats were fed diets containing the same amount of phosphorus but with approximately 63% of it provided as either an organic (poultry, meat, fish meal) or an inorganic source (mono or dibasic sodium phosphate).35 Cats eating the inorganic source of phosphorus had significantly higher concentrations (p<0.05) of phosphate in their urine. Plasma phosphate concentrations also increased in cats eating inorganic phosphorus, while those consuming organic forms of phosphorus remained unchanged. The authors concluded that urinary excretion of phosphate was markedly influenced by diet composition.

A more recent meta-analysis of 14 feline studies and 34 canine studies reported in both species a significant linear relationship between calcium intake and calcium excretion.36 This suggests either the digestion trial may have been too short to induce adaptive mechanisms, or that both dogs and cats do not alter quantitative calcium absorption based on the amount ingested.36 There was less uniformity with regard to phosphorus intake and fecal excretion. The authors interpreted this finding to suggest that other factors, not just dietary phosphorus, influence faecal phosphorus excretion.36 In both species faecal phosphorus excretion was significantly correlated with faecal calcium (p<0.0001), however, the concentration of phosphorus intake did not appear to be an important determinant of true phosphorus digestibility.36 The authors calculated the average digestibility of phosphorus to be 17% in dogs and 31% in cats.36 They reported that the Ca:P had a strong influence on these averages in cats with higher ratios being associated with lower digestibility.36 The average phosphorus digestibility in cats was reported in relation to the Ca:P. It was 49% when the Ca:P was <1.27% when the Ca:P was ≥1 but ≤2, and close to 0% when the Ca:P was >2.36

Other factors can impact phosphorus absorption including intestinal pH, the animal’s phosphorus requirements, phosphorus source, and interactions with other factors in the diet.30,35,37-39 The presence of metabolic acidosis in mice resulted in the upregulation of sodium-dependent transporters. Fractional urinary excretion was increased; however, serum phosphate was not altered.12 Magnesium has also been reported to affect uptake of both calcium and phosphorus.40-43 Hypophosphatemia and hyperphosphatemia both have negative effects. As a result, the body has adapted mechanisms to protect organisms from both extremes and to coordinate the needs for bone mineralization and phosphate homeostasis. Until recently phosphate homeostasis has been viewed to only include PTH and 1,25(OH)2D.64 Parathyroid hormone not only acts primarily to maintain calcium homeostasis, it is also a phosphaturic hormone that decreases renal phosphate reabsorption.13 Parathyroid hormone also stimulates renal conversion of 1,25(OH)2D.65 The major role of 1,25(OH)2D in phosphorus homeostasis is to increase the absorption of phosphorus through the gastrointestinal tract. It also promotes calcium uptake in the intestine and release from bones.31 Together, these hormones regulate both circulating calcium and phosphate.

In response to low-calcium concentrations, the parathyroid gland increases the production and secretion of PTH. Parathyroid hormone then targets the renal distal tubule to inhibit phosphate reabsorption and to stimulate 1,25(OH)2D production through the enzyme 25-hydroxyvitamin D-1-α hydroxylase.11 Subsequently, 1,25(OH)2D increases active calcium and phosphate transport in the gastrointestinal tract.25,45,46 There is also an effect of PTH on bone by PTH receptors in osteoblasts.14 Stimulation leads to an efflux of calcium and phosphate from the bone/fluid compartment and osteoclast-mediated resorption of mineralized bone. The direct influence of PTH on the kidney and bone leads to a restoration of normal serum calcium concentrations. Parathyroid hormone also enhances loss of phosphate through the urine; an effect that offsets vitamin D-mediated absorption of phosphorus through the gastrointestinal tract. The end result is the avoidance of hyperphosphatemia.

Parathyroid hormone and 1,25(OH)2D both stimulate the production of a third phosphorus regulating hormone called fibroblast growth factor 23.14 This hormone is produced and secreted by osteocytes in the bone.67 The main function of this hormone is to promote phosphauria and serve as a counter-regulatory hormone to 1,25(OH)2D.68,69 In humans, certain genetic disorders can result in very high serum concentrations of FGF23. Affected individuals have severe phosphorus wasting, hypophosphatemia, and hypophosphatemic rickets.14,69 Fibroblast growth factor 23 acts as a hormone/systemic factor due to its ability to interact with the FGF receptor in the presence of the alpha-klotho family of proteins.72 In the absence of klotho, FGF23 is not functional and the kidney’s ability to excrete phosphate is
limited contributing to ongoing kidney damage. Together with PTH, FGF23 promotes phosphaturia by decreasing expression of phosphorus transporters in the brush border membrane of the nephron. Fibroblast growth factor 23 is a counter-regulatory hormone for the production of active 1,25(OH)2D by downregulating renal 1-α-hydroxylase. Conversely, a reduction in FGF23 can result in hyperphosphatemia and increased production of 1,25(OH)2D. A negative feedback loop exists between PTH, FGF23 and 1,25(OH)2D. Parathyroid hormone and 1,25(OH)2D can increase FGF23. In turn, FGF23 decreases PTH production and release, and reduces production of 1,25(OH)2D by the kidney. Parathyroid hormone will stimulate 1,25(OH)2D, which in turn downregulates itself and PTH.

Changes in Phosphorus Homeostasis in Chronic Kidney Disease

Chronic kidney disease affects phosphorus because the kidney is the main regulator of phosphorus homeostasis. Alterations to maintain serum phosphate in the normal reference range start early in the disease process in humans and dogs. Data in humans demonstrates that early alterations include an elevation in FGF23, followed by a decrease in 1,25(OH)2D, and then an increase in PTH. Over time the result is an increase in serum phosphate. It has been hypothesized that the elevations documented in FGF23 may be related to a deficiency of the fibroblast growth factor receptor (FGFR) membrane co-receptor klotho. Klotho concentrations decline with age and the progression of chronic kidney disease. A deficiency of klotho leads to FGF23 resistance and ongoing secretion of FGF23 from the osteocytes in bone. In humans, this results in elevations in serum phosphate that are associated with vascular calcifications and death.

Conclusions

Even under normal conditions, phosphorus regulation involves a complicated, multi-organ axis that includes the gastrointestinal tract, kidneys, parathyroid gland, and bone. The parathyroid gland, bone, and kidney are also endocrine organs that produce the hormones that regulate phosphorus. These hormones are PTH, FGF23 and its cofactor klotho, and 1,25(OH)2D. Regulation of phosphorus in the gastrointestinal tract occurs at two levels. The first is a saturable, carrier-mediated transporter component (sodium dependent) that is regulated by 1,25(OH)2D. In addition, phosphorus absorption is also controlled by a non-saturable, concentration-dependent component that is sodium-independent and characterized by paracellular diffusion. Reabsorption of phosphate in the kidney is accomplished by a sodium-dependent, saturable, carrier-mediated transporter. An understanding of the mechanisms that control phosphorus in health is important so that we may understand how to address phosphorus homeostatic changes in disease.

References


Abstract

In the body, phosphorus (P) occurs mainly in the bones but is also known for its central role in energy metabolism and storage with considerable amounts in soft tissues. Major dietary sources of P are proteins, bones, and cartilages as well as inorganic sources added for technical and sometimes nutritional purposes. On the other hand, the organism must be protected against excessive intake or storage of minerals and different strategies exist to eliminate certain elements. With the help of parathyroid hormone (PTH) and other messengers, excessively ingested P is efficiently excreted via urine and therefore usually not considered as a health risk. However, common knowledge in human as well as veterinary medicine is that P is a progressive factor in chronic renal insufficiency (CRI), therefore typically a P-restricted diet is prescribed for affected patients. To date, the total amount of P in a diet is used to assess the daily load of P for the individual. Moreover, excessive P consumption has been shown to have adverse effects on renal, cardiovascular and/or skeletal metabolism, and health in various species. Therefore, P excess is suspected to play a role also in the development of CRI. In 1995, Pastoor demonstrated that a P excess (~890mg P/MJ ME; Ca/P 0.4/1, 28d) reduces the endogenous creatinine clearance in healthy cats. Our studies about the effects of P excess on renal function in cats were performed aiming at verification of these initial findings and at identification of factors influencing the effect of P excess on parameters of kidney function in healthy adult cats such as the calcium-to-phosphorus (Ca:P) ratio or the source of P (inorganic phosphate salts versus “organic” phosphates, e.g., originating from meat and bones).

Phosphorus Metabolism

Major players in the P homeostasis are linked to calcium (Ca) regulation. Briefly, calcium-sensing receptors in the parathyroid gland detect changes in serum Ca concentration, then influencing PTH secretion. PTH increases the Ca blood concentration by increasing bone resorption, tubular reabsorption of Ca in the kidneys, and vitamin D synthesis. Increased bone resorption also raises serum P concentration, while PTH downregulates tubular reabsorption of P. Further modulators of serum P concentrations with phosphaturic effects are fibroblast growth factor 23 (FGF23) and its co-factor alpha-klotho (αklotho). There is possible cross-talk to systems regulating energy metabolism, blood pressure, and even sex hormones. However, species-specific differences probably exist, and a simple extrapolation of findings from man to dogs and cats is not advisable.

However, there is consensus that the prevention of hyperphosphatemia is crucial especially in renal patients to prevent adverse effects on the body, mainly by aiming at limiting the P load per nephron. For example, there is evidence for the role of hyperphosphatemia in transforming cells from vascular phenotype to osteogenic phenotype, creating a predisposition for calcification additionally to the hypothesized direct injury to heart, vessel, and kidney cells.

Phosphorus Excess – Studies Performed in Cats

Since about a decade ago, our research has been performed mainly in cats. For each trial, 12 healthy European shorthair adult cats of both genders, 2 to 8 years old, were available. After a feeding period of 28 days, where the cats were fed a complete and balanced diet based on meat and rice (Ca:P of 1.3/1), the cats were randomly allocated to either a control or a test group, respectively. For another period of 28 days, one group of six cats stayed on the control diet, and the other six cats received the same diet with a surplus of P from different “organic” and inorganic sources (adding up to a total of ~880mg/MJ ME) and a Ca:P ratio of either 0.4/1, 0.9/1 or 1.3/1 in the test animals (crossover design). A balance study was carried out in the final 10 days of each test period. Endogenous creatinine clearance, blood chemistry, urine analysis, and water and mineral balance were determined. With these trials we were able to show that P excess might cause — among other findings — a decrease in endogenous creatinine clearance, glucosuria, hematuria, and an increase in renally excreted P, and therefore the P load per nephron, depending on factors such as the source of P and the Ca:P ratio already after short-term exposure to added amounts of P, from certain sources.
Phosphorus Excess – Studies Performed in Dogs

Aiming at insight about P kinetics after oral supply with different amounts and sources of P in dogs, additional trials in dogs were started in 2012. In eight adult Beagles, the apparent digestibility (aD) of P and Ca was determined after feeding a control diet (0.5% P/DM) for 18 days (13 days adaptation, 5 days balance). This was repeated aiming at 2.2% P/DM by adding different phosphates (e.g., CaHPO4, NaH2PO4, poultry meal, Na5P3O10, Ca(H2PO4)2, bone meal, KH2PO4, K4P2O7), while adjusting the Ca:P ratio to ~1:3:1 using CaCO3 with washout periods of ≥10 days. Serum P, Ca, and PTH were determined at day 18 (preprandially and two hours postprandially). Preprandial and postprandial urine was analyzed for creatinine and P.

Postprandial serum P concentrations increased significantly with levels above the reference range in NaH2PO4, Na5P3O10, Ca(H2PO4)2, KH2PO4, K4P2O7 but not in rations with P from organic sources. Postprandial PTH levels clearly increased especially in diets with Na and K phosphates (NaH2PO4, Na5P3O10, KH2PO4, K4P2O7) and Ca(H2PO4)2.

Based on these results, the effects of an oral load of P from different sources on the kinetics of P and related serum parameters were studied in eight healthy Beagles (3±1y; 14±1kg BW) in more detail. The study design was kept identical to the first trial in dogs, but on day 18 blood was sampled one hour (h) preprandially as well as 0.5, 1, 1.5, 2, 3, 5, and 7 hours postprandially. Serum was analyzed among others for minerals and PTH; AUCs were calculated (AUC0.5-7). With this study, we were able to verify the former findings of higher aD and much stronger effects of Pi sources on postprandial serum P and PTH concentrations than organic P from bony material. Especially KH2PO4 led to a significant increase of both serum P and PTH with a peak three hours postprandially. The serum Ca×P product exceeded the recommended threshold of 55mg2/dl2 up to 2.1-fold in dogs fed Pi. Feeding these Pi sources in excess to dogs changed the kinetics of serum P and PTH with a prolonged increase of both parameters, possibly disrupting the Ca and P balance. The aD of P, sources, which are highly water soluble (Lineva, et al., 2017), correlates with serum P and PTH concentrations.

Conclusion

Because of the relevance of the P load in CRI patients and obviously also in clinically healthy animals due to the potentially adverse effects of elevated serum P and PTH levels on skeleton, cardiovascular system, and kidneys, the intake of highly soluble P compounds such as Na and K phosphates have to be assessed separately. Knowledge of the total amount of P in a diet does not suffice to decide about adequacy or potential adverse effects. Further work on factors influencing the effects of P on the body, such as other minerals in the diet, Ca:P ratio, cation-anion-balance, urine volume, and species-specific effects, etc., are clearly warranted.

References


Notes
Phosphorus is essential for life and an important nutrient component for both felines and canines. Interestingly, different pet diets can vary in their content of phosphorus, yet the quantity of phosphorus in the food is not always on the product package. Since dietary phosphorus intake varies, there must be a system to maintain phosphorus balance in the body. In dogs, cats, and humans, the kidneys are responsible for regulating phosphorus homeostasis. When phosphorus intake is limited, the kidneys conserve phosphorus, and when phosphorus intake is excess, the kidneys increase elimination of phosphorus into the urine. However, because pet foods contain phosphorus for a variety of purposes beyond nutrition, pet diets are unlikely to be deficient in phosphorus but more commonly adequate or high in phosphorus. Because current commercial feline diets typically contain adequate to high phosphorus amounts, the kidneys are predominantly required to extract excess phosphorus and deliver it into the urine. However, should a cat (or dog) continue to consume a diet containing excessive phosphorus and also develop kidney functional impairment, the pet is likely to develop positive phosphorus balance.1

If this positive phosphorus balance persists over time, the likely outcome is further kidney injury and, in some instances, chronic kidney disease (CKD).2 While an important goal in CKD is to minimize phosphorus retention in the body, it is important to recognize that fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH) are effective in keeping, or perhaps “hiding,” serum phosphorus concentration until the later stages of CKD. Nonetheless, persistent activation of FGF23 and PTH, even in early CKD stages, have been linked to earlier mortality.3 These activities during IRIS CKD Stages 1 and 2 essentially hide the damage developing in the kidneys because our diagnostic tools, such as serum creatinine concentration and urine concentration ability, are usually “within or just above the normal range.” It appears that IDEXX SDMA™ testing is a significant improvement in detecting early kidney disease, particularly in IRIS CKD Stage 1. In the near future, new renal biomarkers may be able to identify ongoing kidney injury even earlier. The future may allow us to slow or stop many renal injuries that evolve from excess phosphorus well before the patient enters IRIS CKD Stage 3 where the ability to stop progression of CKD can be challenging.

**When (and If) Should Dietary Phosphorus Intake Be Restricted?**

Evidence suggests that feeding a diet daily containing excessive phosphorus for an extended period may lead to CKD.1 The concern of excessive phosphorus intake leading to progression of CKD is realistic if the pet already has early CKD, even in IRIS CKD Stages 1 and 2. Therefore, limiting phosphorus intake for dogs and cats with CKD at any level of CKD needs to be further studied. The IRIS has developed targets based on a combination of the patient’s IRIS CKD stage and the patient’s serum phosphorus concentration (Tables 1 and 2). The goal is to keep the pet’s serum phosphorus concentration within the recommended IRIS CKD stage targets with the hope that phosphorus-associated injuries will be minimized. Monitoring the serum phosphorus concentration is a logical basis for the targets in that an elevated serum phosphorus concentration is direct evidence of excessive phosphorus retention.4

To confirm that the dietary phosphorus intake is appropriate for the patient, measure the serum creatinine and phosphorus concentrations when well hydrated and fasted in the past 12 hours.

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**Table 1. IRIS CKD Stage (Based on Serum/Blood Creatinine Concentration)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Dogs Serum Creatinine</th>
<th>Cats Serum Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>µmol/l mg/dl</td>
<td>µmol/l mg/dl</td>
</tr>
<tr>
<td>At Risk</td>
<td>&lt;125 &lt;1.4</td>
<td>&lt;140 &lt;1.6</td>
</tr>
<tr>
<td>1</td>
<td>&lt;125 &lt;1.4</td>
<td>&lt;140 &lt;1.6</td>
</tr>
<tr>
<td>2</td>
<td>125 – 180 1.4 – 2.0</td>
<td>140 – 250 1.6 – 2.8</td>
</tr>
<tr>
<td>3</td>
<td>181 – 144 2.1 – 5.0</td>
<td>251 – 440 2.9 – 5.0</td>
</tr>
<tr>
<td>4</td>
<td>&gt;440 &gt;5.0</td>
<td>&gt;440 &gt;5.0</td>
</tr>
</tbody>
</table>

www.iris-kidney.com
The creatinine concentration defines the pet’s IRIS CKD stage and the phosphorus concentration is used to confirm whether the phosphate is within the phosphorus target range (Tables 1 and 2). If the serum phosphorus concentration exceeds the phosphorus target, then change to a lower phosphorus diet and/or a phosphorus binder (see below) as indicated. Every time a change in diet or enteric phosphorus binder is made (e.g., dose or different binder), the same sampling is repeated, but two to six weeks after the change has been made so that the effectiveness of the new prescription is meeting the targets. These adjustments should be repeated in the same way until the target is achieved. Once the phosphorus target is achieved, they should be re-evaluated every three to four months to determine the prescription is still correct or needs a therapy change.

**Phosphorus Restriction: Dietary Changes and Enteric Phosphorus Binders**

Reducing excessive phosphorus in the body is performed by reducing the amount of phosphorus that can be absorbed from the intestines into the body. The first step should always be to modify the food to a low-phosphorus diet. Higher doses of enteric phosphorus binders (EPB) can cause unwanted side effects and/or adversely effect on food (less palatable). Since EPBs have limited maximum ability to bind phosphorus, the EPBs will be most efficient when used after the patient is already consuming a low-phosphorus diet.

**Phosphorus Reduced Diet.** While there are several canine and feline diets that have relatively low-phosphorus content, renal diets (commercial or formulated by board-certified veterinary nutritionists) are usually the most effective in limiting phosphorus retention. Some nutritionists recommend geriatric diets that are relatively low in phosphorus and they may be reasonable for patients in IRIS CKD Stage 1.

For dogs and cats with IRIS CKD Stages 3 and 4, it is appropriate to start with selecting a diet formulated specifically for CKD. These diets are generally the most restricted phosphorus diets available, and achieving the phosphorus target in patients with Stages 3 and 4 can be challenging. Further, these patients typically benefit from characteristics of these diets that are specifically formulated to address the clinical consequences of patients with IRIS CKD Stages 3 and 4.

Introducing renal diets to dogs and cats, particularly those in advanced stages of CKD, requires patience and gradual introduction to the diet. Typically, dogs require a few days to two weeks for diet change, while cats may require two to four weeks or more to accept the new diet. For some patients, mirtazapine or capromorelin can be very useful for enhancing the accepting of the new diet.

**Enteric Phosphorus Binders.** Enteric phosphorus binders can improve control of phosphorus when renal diets alone have failed to achieve the phosphorus target. The goal with EPBs is to prevent dietary phosphorus delivered to the intestine from being absorbed into the blood. Administered orally, aluminum, calcium, and lanthanum form insoluble complexes with phosphorus within the lumen of the intestine thereby hindering adsorption of phosphorus and reducing serum phosphorus concentration. Several forms of intestinal phosphorus binders are available for use in dogs and cats: aluminum hydroxide, aluminum carbonate, calcium carbonate, calcium acetate, and lanthanum carbonate are among options for EPBs for dogs and cats. In choosing an EPB, consider effectiveness, acceptance to the patient, cost, and potential adverse side effects.

It is essential that the pet owner understand how the EPB works and how to administer the binder, or they are unlikely to be effective. In order to bind phosphorus in the diet, the diet and the EPB must be present in the gastrointestinal system at the same time. If food is not present with the EPB, the food’s phosphorus will be free to be absorbed. Thus, to maximize effectiveness, it is important for the EPB and the food to be together at the same time. If it is not possible to give the EPB and food together, administer the EPB as closely as possible to provide one hour either direction from the meal.

The most effective EPB used in dogs and cats are aluminum binders. They are effective and affordable, several forms are available, and usually they have few adverse effects if the dosage does not exceed the recommended dosages. It is available as powder, capsules, and flavored (mint) liquids. The powder form has the benefit that it mixes into the food to assure delivery and interaction with the food. I recommend starting with an aluminum EPB.

Administer EPBs starting with a dose of 30 to 60 mg/kg/day divided into portions according to the percentage of daily food. Ideally, mix the EPB into the food. Remeasure the serum creatinine and phosphorus concentrations after four to six weeks. Determine whether the serum phosphorus concentration meets or is below the target according to the IRIS CKD Stage defined by the concurrent measured serum creatinine concentration. In addition, examine for any signs of toxicity of the aluminum EPB that have developed. Look for evidence of aluminum adverse effects including signs in

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<table>
<thead>
<tr>
<th>Patient’s IRIS CKD Stage</th>
<th>Serum Phosphorus Range*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmol/l</td>
</tr>
<tr>
<td>IRIS CKD Stage 1:</td>
<td>0.81 - 1.45</td>
</tr>
<tr>
<td>IRIS CKD Stage 2:</td>
<td>0.81 - 1.45</td>
</tr>
<tr>
<td>IRIS CKD Stage 3:</td>
<td>0.81 - 1.61</td>
</tr>
<tr>
<td>IRIS CKD Stage 4:</td>
<td>0.81 - 1.94</td>
</tr>
</tbody>
</table>

* Plasma phosphorus concentration should remain from the target or lower.

www.iris-kidney.com
the brain, blood, and muscle — particularly microcytosis, muscle weakness, or neurological signs. If toxicity appears to be present, consider changing to a different EPB. The maximum dosage for aluminum EPBs is 90 mg/kg/day.

If the target has not achieved on the first month but no EPB complications have developed, increase the dosage and follow-up as described previously. The dosage can be increased until the goal is achieved or the aluminum-EBC exceeds 90 mg/kg/day. It is possible to mix EPBs, but the risk of side effects increases.

References
Formulation of nutritionally complete pet food often necessitates the addition of phosphorus to meet the phosphorus requirement of the pet and to balance the calcium/phosphorus ratio of the food. However, phosphorus has several other important functions. Sodium and calcium phosphates are used as processing aids, helping to ensure optimal cooking and texture of the food. Phosphates may also be used to control urine pH or to reduce the accumulation of dental tartar.

Many phosphorus sources are approved for use in pet, livestock, and human food. Inorganic sources of phosphorus used in pet food include calcium phosphates, sodium phosphates, bone meal, deflourinated phosphate, and phosphoric acid. Manufacturers choose phosphorus sources based on the intended functionality. Some commonly used inorganic phosphorus sources are listed in Table 1.

The chemical form of phosphorus can affect its functionality and bioavailability as a nutrient. Bioavailability is defined as “the degree to which an ingested nutrient in a particular source is absorbed in a form that can be utilized by the animal.” Factors affecting bioavailability include absorption, excretion, and ability to be utilized for a specific physiological function. The bioavailability of phosphorus varies by source and is influenced by calcium content of the diet. Plant-based food ingredients typically have very poor phosphorus bioavailability. In contrast, inorganic sources of phosphorus, including meat meals, fish meal, bone meal, and inorganic phosphate supplements, are more highly bioavailable.

<table>
<thead>
<tr>
<th>Name</th>
<th>Alternate Names</th>
<th>Chemical Composition</th>
<th>Use in Pet or Human Food Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium Phosphates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium Phosphate</td>
<td></td>
<td>$\text{Ca}_3(\text{PO}_4)_2$</td>
<td>Nutritional source of Ca, P General purpose food additive, texture</td>
</tr>
<tr>
<td>Dicalcium Phosphate</td>
<td>Calcium phosphate dibasic</td>
<td>$\text{CaHPO}_4$</td>
<td>Nutritional source of Ca, P</td>
</tr>
<tr>
<td></td>
<td>Dibasic calcium phosphate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcium monohydrogen phosphate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcium hydrogen phosphate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monocalcium Phosphate</td>
<td>Calcium acid phosphate</td>
<td>$\text{CaH}_4(\text{PO}_4)_2$</td>
<td>Nutritional source of Ca, P Sequestrant</td>
</tr>
<tr>
<td></td>
<td>Calcium biphosphate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Monobasic calcium phosphate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcium dihydrogen phosphate</td>
<td></td>
<td></td>
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<tr>
<td>Tricalcium Phosphate</td>
<td>Calcium phosphate tribasic</td>
<td>$\text{Ca}_3(\text{PO}_4)_2$</td>
<td>Nutritional source of Ca, P</td>
</tr>
<tr>
<td></td>
<td>Tribasic calcium phosphate</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Tricalcium hydrogen phosphate</td>
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<td>Sodium Phosphates</td>
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<tr>
<td>Monosodium Phosphate</td>
<td></td>
<td>$\text{NaH}_2\text{PO}_4$</td>
<td>Processing aid</td>
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<tr>
<td></td>
<td>Monobasic sodium phosphate</td>
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<tr>
<td></td>
<td>Sodium dihydrogen phosphate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sodium phosphate monobasic monohydrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium Acid Pyrophosphate</td>
<td></td>
<td>$\text{Na}_2\text{H}_2\text{P}_2\text{O}_7$</td>
<td>General purpose food additives Processing aid Leavening agent</td>
</tr>
<tr>
<td>Name</td>
<td>Alternate Names</td>
<td>Chemical Composition</td>
<td>Use in Pet or Human Food Products</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----------------</td>
<td>----------------------</td>
<td>-----------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Sodium Phosphates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium Hexametaphosphate</td>
<td>Hexasodium metaphosphate</td>
<td>(NaPO_{3})<em>{x}·H</em>{2}O \ (x = 6-20)</td>
<td>Tartar control agent coated on dry food products for reducing the accumulation of dental tartar in dogs and cats Sequestrant</td>
</tr>
<tr>
<td>Sodium Tripolyphosphate</td>
<td>Sodium phosphate tribasic Sodium tripophosphate STPP</td>
<td>Na_{3}PO_{4}</td>
<td>General purpose food additive Processing aid Sequestrant</td>
</tr>
<tr>
<td>Tetrasodium Pyrophosphate</td>
<td>Pyrophosphate Sodium pyrophosphate TSPP</td>
<td></td>
<td>Processing aid Sequestrant Dispersant</td>
</tr>
<tr>
<td>Other</td>
<td>Bone Meal</td>
<td>(Ca_{5}(PO_{4})_{3}(OH))</td>
<td>Nutritional source of Ca, P</td>
</tr>
<tr>
<td></td>
<td>Defluorinated Phosphate defluorinated</td>
<td>includes either calcined, fused, precipitated or reacted calcium phosphate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phosphoric Acid Orthophosphoric acid</td>
<td>H_{3}PO_{4}</td>
<td>Acidifier (urine) General purpose food additives</td>
</tr>
<tr>
<td></td>
<td>Trace Mineral Phosphates</td>
<td>Examples: Copper orthophosphate Copper pyrophosphate Iron phosphate Iron pyrophosphate Manganese orthophosphate Manganese phosphate</td>
<td>Nutrient source</td>
</tr>
</tbody>
</table>

References
Notes
Notes
Appendix

2019 CAN Summit
The Science Of Cats

DR. WESLEY WARREN
Dr. Warren received his BS degree in Animal Sciences from Oklahoma State University in 1984, his MS degree in Reproductive Physiology from Clemson University in 1987, and a PhD from the University of Missouri in Molecular Endocrinology in 1990. He completed a post-doctoral fellowship at G.D. Searle Pharmaceutical before joining Monsanto Company in 1991 where, from 1992 to 1999, he held several leadership roles including group manager of genome initiatives. Dr. Warren joined the McDonnell Genome Institute in 2001 where he held various appointments as Assistant Director, Associate Professor of Genetics, and a secondary appointment in Molecular Microbiology, both in the Washington University School of Medicine and affiliate scientist position at the St. Louis Zoo. Dr. Warren is currently a Professor of Genomics at the Bond Life Sciences Center and he is an internationally recognized expert in animal comparative genomics.

DR. MARGARETHE HOENIG
Dr. Margarethe Hoenig received her DVM and a Dr.med.vet. degree from the Veterinary School in Hannover, Germany. She also received a PhD degree from the University of Pennsylvania School of Medicine Diabetes Center. She completed a rotating internship at UC Davis, a small animal internal medicine residency at the University of Pennsylvania, and a postdoc in Pharmacology at Cornell University. She was a Professor of Physiology, Pharmacology and Small Animal Medicine at the University of Georgia and a Professor of Small Animal Medicine at the University of Illinois. She is now an Emeritus Professor. She has published and lectured extensively in the area of feline endocrinology and metabolism and has received numerous research awards.

DR. PAUL D. PION
Dr. Paul D. Pion holds a BS and a DVM from Cornell University. He is a Diplomate of the American College of Veterinary Internal Medicine (Specialty of Cardiology). He interned at the Animal Medical Center in New York City, completed a residency in Cardiology at UC Davis, a post-doctorate in Pharmacology at Columbia University, and coursework and research toward his PhD at UC Davis. Dr. Pion cofounded Veterinary Information Network (VIN) in 1991. He is the Chief Executive Officer, President, and a director of VIN. He was a full-time instructor and researcher at UC Davis where he was responsible for breakthrough research on nutrition and heart disease in cats. Dr. Pion has published extensively, including a cover article for the journal “Science” announcing the identification of taurine deficiency as a major cause of dilated cardiomyopathy in cats which led to near elimination of the disease via reformulation of commercial feline diets.

DR. ROBERT BACKUS
Dr. Robert Backus is an Associate Professor and Director of Nestlé Purina Endowed Program in Small Animal Nutrition in the College of Veterinary Medicine at the University of Missouri, Columbia campus. He graduated from UC Davis, School of Veterinary Medicine in 1987 and earned MS and PhD degrees in Physiology at the University in 1987 and 1991, respectively. While at UC Davis, he began his study of small animal nutrition as a post-doctoral fellow investigating causes of taurine deficiency in cats. Dr. Backus became a research faculty member in the Department of Molecular Biosciences and Director of the Feline Nutrition and Pet Care Center at UC Davis. Currently, he continues as Director of the Endowed Program, maintains an active research program, and co-supervises with an ACVN-boarded faculty member offering clinical nutrition consulting, training of residents, and offerings of elective rotations in clinical nutrition to veterinary professional students.

DR. DAVID THOMAS
Dr. David Thomas obtained a Bachelor of Science Honours degree in Zoology from Dundee University in 1990, and a PhD from the Institute of Zoology, which was part of University College London in 1994. He moved to New Zealand in 1995 to take up a two-year Massey University/AgResearch Post-Doctoral Fellowship, and he joined the teaching staff at Massey University in 2003. Dr. Thomas was appointed as Director of the Centre for Feline Nutrition in 2004 responsible for overseeing commercial and applied nutrition research, and has since established research programmes in Canine and Equine Nutrition. Currently he is an Associate Professor in Companion Animal Science in the School of Agriculture and Environment.

DR. NICK CAVE
Dr. Nick Cave graduated from Massey University in 1990 with a BVSc, and worked in general practice for 6 years until 1997, when he returned to Massey for a residency in...
small animal internal medicine and attained membership in the Australasian College of Veterinary Scientists by examination. He graduated with a Masters in Veterinary Science in 2000. In 2004, he moved to UC Davis, where he attained a PhD in Nutrition and Immunology. At the same time, he completed a residency in Small Animal Clinical Nutrition. In late 2005, he returned to Massey University as Senior Lecturer in Small Animal Medicine and Nutrition. He has authored more than 30 peer-reviewed publications and is on the editorial board for the “Veterinary Quarterly” and “Veterinary Education International.” He is a founding member of the WSAVA Nutritional Guidelines Committee.

Dr. Séverine Ligout
Dr. Séverine Ligout earned a pre-doctorate diploma in Neurosciences, Behavior, and Cognition from the University Paul Sabatier, Toulouse (France) and a PhD in Animal Behavior from the University François Rabelais, Tours (France). Prior to joining Nestlé Purina, she held several post-doctoral positions in France [National Institute for Agricultural Research (INRA), National Center for Scientific Research (CNRS), University of Saint-Étienne] and in the UK (University of Lincoln). These positions allowed her to gain further expertise in the areas of social preferences, animal cognition, welfare, acoustic communication, and human-animal bond. Dr. Ligout is a Senior Scientist in Behavior & Welfare research at Nestlé Purina. Since joining Nestlé Purina in 2011, her work has focused on understanding the feeding behavior of cats and dogs. Her research activities have mainly focused on better elucidating how pets express their food enjoyment and how feeding behaviors can be impacted by specific product characteristics.

Dr. Ken Lambrecht
Dr. Ken Lambrecht received his DVM from the University of Missouri in 1981. He has been the Medical Director and owner of West Towne Veterinary Center in Madison, WI which has been AAHA accredited since 1995 and a Gold Level Designated Cat Friendly Practice since 2015. He currently serves on the AAFP Board of Directors and has previously served on the AAHA, Marketlink and PNA Boards. He was a coauthor of the “AAHA 2012 Canine Life Stage Guidelines.” He is a current member of the PNA Educational Tools Committee. His primary interests are feline medicine, dentistry, and preventive nutrition — in particular obesity prevention and management. He is the Medical Director of Pets Reducing for Rescues which, in its 10-year history, has raised over $18,000 for local rescues. His adventure cat, Bug, accompanies him on almost all travels!

Dr. Andrea J. Fascetti
Dr. Andrea J. Fascetti graduated from the University of Pennsylvania, School of Veterinary Medicine. Following graduation she completed an internship and medicine residency at The Animal Medical Center in New York City. She holds a doctoral degree in nutrition from UC Davis. Dr. Fascetti is a Diplomate of both the American College of Veterinary Internal Medicine and the American College of Veterinary Nutrition. Andrea is currently a Professor of Nutrition at UC Davis. She is the Scientific Director of the Feline Nutrition and Pet Care Center and the Amino Acid Laboratory. She received the AVMF/Winn Feline Foundation Excellence in Feline Research award in 2016. Her current research interests are amino acid and trace mineral metabolism, obesity, carnivore nutrition, nutritional idiosyncrasies of the cat, improvement of pet foods and clinical nutrition.

Dr. Britta Dobenecker
Dr. Britta Dobenecker is Vice Head of the Chair of Animal Nutrition and Dietetics, Department of Veterinary Sciences, Ludwig Maximilians Universität München. She graduated from Veterinary School in Hannover, Germany with a doctoral thesis on energy metabolism in obese cats. She is certified as a Veterinary Specialist (Fachtierärztin) for Animal Nutrition and Dietetics (national). Dr. Dobenecker is board-certified (European Specialist in Veterinary and Comparative Nutrition; European College of Veterinary and Comparative Nutrition), and serves as an Assistant Professor (Akademischer Oberrätin) and Chair of Animal Nutrition and Dietetics, Department of Veterinary Sciences, Ludwig Maximilians Universität München, Germany. She is currently Vice President of the European Society of Veterinary and Comparative Nutrition.

Dr. David Polzin
Dr. David Polzin is a Professor at the University of Minnesota College of Veterinary Medicine. He received his veterinary degree from the University of Illinois College of Veterinary Medicine in 1975. He completed an internal medicine residency at the University of Georgia College of Veterinary Medicine in 1981 and is a Diplomate of the American College of Veterinary Internal Medicine. Later that year, Dr. Polzin returned to the University of Minnesota to complete his doctorate in Veterinary Medicine. He is a distinguished author and speaker.

Dr. Gail Czarnecki-Maulden
Dr. Gail Czarnecki-Maulden is a Senior Research Nutritionist at the Nestlé Research Center in St. Louis. She received a doctorate degree in Animal Nutrition from the University of Illinois. Before joining Nestlé Purina, Dr. Czarnecki-Maulden was Associate Professor of Companion Animal Nutrition at the University of Illinois. She is a member of both the National Academy of Science Board on Agriculture and Natural Resources and the Association of American Feed Control Officials (AAFCO) Dog and Cat Nutrient Profiles Subcommittee.
She has served as a member of the Scientific Advisory Board of the International Probiotics Association and the Division of Nutritional Sciences External Advisory Board of the University of Illinois. Dr. Czarnecki-Maulden has published over 75 articles and abstracts on pet nutrition based on her research related to mineral and amino acid metabolism and the effect of nutrition on gastrointestinal health.
Notes