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Feline Diabetes Mellitus: Low Carbohydrates Versus High Fiber?

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NUTRITIONAL GOALS

Diabetes mellitus (DM) can be classified into multiple subtypes; however, most feline diabetics are either type I (insulin-dependent DM) or type II (non–insulin-dependent DM) [1,2]. In the cat, type II DM seems to predominate, despite the need for exogenous insulin therapy. More than 80% of cats are thought to have type II DM, with the remaining cases thought to be secondary to other conditions, such as carcinoma, pancreatitis, or acromegaly. Type II DM has been referred to as a relative insulin deficiency because the amount of insulin actually secreted may be increased, decreased, or normal but is always inadequate relative to serum glucose levels. In cats, DM is characterized by peripheral insulin resistance combined with dysfunctional β cells. Cats with type II DM require oral hypoglycemic drugs or exogenous insulin coupled with nutritional management [2].

The goals of nutritional management in DM are to (1) blunt postprandial hyperglycemia, (2) control body weight, (3) support altered nutrient needs, (4) improve peripheral insulin sensitivity, (5) avoid diabetic complications (eg, hypoglycemia, ketosis, neuropathies), and (6) coordinate peak nutrient uptake with insulin activity. More recently, another goal, achieving diabetic remission, has come to the forefront of the nutritional plan. Pharmaceutic treatment combined with an appropriate food composition and feeding plan should optimize glycemic control, control weight, and result in remission in most cats.

ETIOPATHOGENESIS OF TYPE II DIABETES

The deposition of islet amylin and progressive β-cell destruction are characteristic of type II DM in people and cats [3,4]. Amylin is formed from islet amyloid polypeptide (IAPP), a peptide cosecreted with insulin. In people, chronic β-cell stimulation and increased IAPP release occur after high simple carbohydrate intake and peripheral insulin resistance. Increased pancreatic amyloid deposition is associated with impaired glucose tolerance [3–5]. This same phenomenon seems to occur in cats [3–6]. As true carnivores, evolutionary adaptations

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have altered the cat's use of and tolerance to dietary carbohydrates [7]. The phenomenon of insulin resistance and carbohydrate intolerance has been referred to as the "carnivore connection" [8]. During the Ice Ages, when human beings consumed a meat-based low-carbohydrate diet, metabolic adaptations limited insulin's effect to sustain blood glucose levels [6,8]. Cats, having adapted to a meat-based diet, have also evolved to maintain blood glucose in the face of low carbohydrate intake. In the cat, these adaptations have resulted in constant hepatic glucose production from amino acids (gluconeogenesis) and delay in carbohydrate use (low glucokinase activity) [7]. Unfortunately, factors that lead to prolonged elevation of plasma glucose (ie, impaired insulin secretion, insulin resistance) can lead to diabetes. Chronic hyperglycemia and insulin resistance promote hypersecretion of insulin, which may lead to β-cell exhaustion. In addition, chronic hyperglycemia causes hydropic degeneration of the feline β cell ("glucose toxicity") [9]. Both mechanisms contribute to decreased pancreatic insulin secretion in cats.

Insulin resistance seems to be a key driving force in the development of type II DM in people and cats [10,11]. Downregulation and postreceptor defects of peripheral glucose receptors (GLUT 4 receptors) on muscle and adipose tissue result in decreased glucose disposal in response to normal levels of circulating insulin [11]. Progressively greater insulin release is required to achieve euglycemia. The process becomes a vicious cycle. Obesity promotes insulin resistance, which, in turn, increases β-cell release of insulin, cosecretion of IAPP, pancreatic amyloid accumulation, hyperglycemia, and glucose toxicity. Eventually, the triad of β-cell exhaustion, glucose toxicity, and insulin resistance progresses to overt DM [4,5,10,11].

Recent studies have described large proportions of diabetic cats in which nutritional management and pharmacologic therapy have resulted in resolution of the diabetic state [12–15]. These transient diabetics presumably have regained β-cell function following reversal of glucose toxicity and/or improved peripheral insulin resistance. The rate of transient diabetes seems to be increasing with the advent of new diet strategies and insulin therapy. Whereas transient diabetes was reported to occur in 10% to 25% of feline diabetics, DM may be transient in upward of 50% to 70% of cats [15].

DM affects cats of any age and gender but is diagnosed more commonly in neutered male cats older than 6 years of age, which is the same population most at risk for obesity (Table 1) [16,17]. In the cat, obesity has been shown to result

Table 1
Comparison of risk factors for obesity and diabetes mellitus in the cat

Obese	Diabetes mellitus
Advancing age	Advancing age
Male	Male
Neutered	Neutered
	Obesity

in abnormal glucose tolerance and peripheral insulin resistance [18–20], factors that are known to precede the development of type II DM in cats and people. The risk of developing DM increases by nearly fourfold in obese cats [17]. Weight loss reduces insulin resistance and is an important component in managing DM.

NUTRITIONAL FACTORS IN FELINE DIABETES MELLITUS

Diet composition, form, and feeding methodology can have a significant impact on diabetic regulation. When choosing a food to manage the diabetic cat, concentrations of key nutrients that may alter regulation should be considered. Traditionally, fiber-fortified foods have been recommended in the management of feline DM. The advantages include weight control and slowed glucose uptake from the intestines. Low-carbohydrate foods are now considered superior for the management of DM and have even been suggested as preventative [14,15,21]. It is important to remember that several nutrient classes vary when changing from a traditional low-fat high-fiber food to a low-carbohydrate high-protein food. Such factors as energy density, protein, and micronutrient concentration may all be affected.

Energy

Cat with DM often present with a history of significant weight loss yet are often overweight or obese [16]. Before making recommendations for daily energy requirements (DERs), it is important to emphasize that the clinical response to nutritional management of the diabetic cat is highly dependent on satisfactory medical management with insulin or oral hypoglycemic drugs and weight control. Traditional fiber-fortified foods designed for weight control (3.5 kcal/g dry matter metabolic energy [ME]) are appropriate for weight reduction and glycemic control in overweight cats. Good results can be achieved with appropriate patient compliance, which is sometime easier to achieve when feeding the larger food volume afforded by fiber-fortified foods. Recent studies suggest that cats regulate food intake by volume, and fiber-fortified foods reduce caloric intake [22].

In underweight cats or those with poor tolerance to dietary fiber, higher energy foods are more appropriate (4.0–4.5 kcal/g dry matter ME). In these cats, the low-carbohydrate foods, with their reduced fiber and increased fat and calorie content, are good alternatives.

Protein

Diabetic animals occasionally may have increased loss of amino acids in urine attributable to inappropriate or inadequate hormonal signals and glomerulonephropathies. More commonly, loss of lean body mass is attributable to inadequate insulin concentrations, with poor cellular amino acid uptake and increased protein metabolism via hepatic gluconeogenesis. Diabetic cats require high-quality protein of good biologic value. Protein content of the food should be greater than 30% dry matter of the food and greater than 85% digestible. Newer low-carbohydrate high-protein foods supply relatively similar protein levels to those of high-fiber formulas when determined as a percent of ME

intake (Table 2). In the face of limited dietary carbohydrates, higher protein levels are theoretically required to support increased hepatic gluconeogenesis and normal blood glucose production. Failure to maintain blood glucose because of high glucose demands and insufficient hepatic gluconeogenesis has only been reported during gestation and lactation in the cat [23]. In adult cats, published protein requirements already account for sustained gluconeogenesis and increased protein metabolism [24]. Thus, the absolute protein requirement for the adult diabetic cat is unlikely to be significantly higher than adult maintenance requirements [24] and would certainly be less than the average protein content of most commercial feline foods. Nonetheless, when lowering the overall carbohydrate content of a diet, fat, protein, or both must increase to account for the difference. Because fat is known to increase insulin resistance and decrease glucose tolerance, it is logical to replace carbohydrates with protein as opposed to fat [25].

The total amount of protein is only modestly increased in newer low-carbohydrate foods compared with traditional high-fiber foods. Nevertheless, there are certain conditions in which this increased protein may be contraindicated. Cats with concurrent renal disease typically experience increased blood urea nitrogen when switched to a higher protein diet. It has been suggested by some that an increased glomerular filtration rate (GFR) in response to higher protein intake or alleviation of diabetic nephropathy actually improves renal function in diabetic cats. The implication is that limiting dietary protein in diabetic cats with renal disease may be unnecessary. Although protein does not promote renal failure, it is the author's experience that cats having blood urea nitrogen values greater than 50 mg/dL when eating a high-protein low-carbohydrate food often demonstrate a better attitude and appetite when switched to a lower protein renal therapeutic diet. To continue limiting carbohydrate use, adding acarbose therapy (12.5 mg/cat twice daily with a meal) to the new diet has sustained the benefit of low-carbohydrate intake.

Using low-carbohydrate diets in cats with pancreatitis is also contraindicated according to some product guides. Because cholecystokinin (CCK) is

Table 2
Nutrient comparisons for selected therapeutic foods designed to manage feline diabetes mellitus (% dry matter [g/per 100 kcal])

Food type[a]	Protein	Fat	Nitrogen free extract	Crude fiber
Hill's w/d can	40 (12)	17 (4.8)	26 (7.6)	11 (3.1)
Hill's w/d dry	39 (11)	9.6 (2.7)	38 (11)	7.4 (2.1)
Hill's m/d can	53 (13)	19 (4.8)	16 (3.9)	6.0 (1.5)
Hill's m/d dry	52 (12)	22 (5.2)	16 (3.6)	5.5 (1.4)
Royal Canin DS 44 dry	49 (12)	13 (3.2)	26 (6.4)	5.3 (1.3)
Purina DM can	57 (12)	24 (5)	8 (1.7)	3.6 (0.8)
Purina DM dry	58 (13)	18 (4)	15 (3.3)	1.3 (0.3)

[a]Hill's Pet Nutrition, Inc., Topeka, Kansas; Nestlé Purina PetCare Company, St. Louis, Missouri; Royal Canin USA, Inc., St. Charles, Missouri.

maximally secreted by proteins, amino acids, and fat, the use of moderate-protein, low-fat, and high-carbohydrate foods has been recommended. This is an area of great uncertainty. Many cats with chronic pancreatitis are well maintained on recovery type diets (high-protein, high-fat, and low-carbohydrate foods). Regardless, current food recommendations for cats with acute and/or active pancreatitis are intestinal therapeutic foods having a larger portion of the calories obtained from carbohydrates.

Finally, cats with severe liver disease and hepatoencephalopathy, or those at reasonable risk of hyperammonemia, should not be fed these high-protein foods.

Carbohydrates

The ideal composition and quantity of carbohydrates in foods for management of DM in people and cats remain controversial. Diets containing up to 85% carbohydrates have been recommended in people, with the bulk containing highly complex carbohydrates and soluble fibers [26]. Significantly lower levels of carbohydrates (<10%–20% dry matter) have been recommended for diabetic cats because of their nutritional peculiarities as an obligate carnivore [27]. The optimal level of soluble carbohydrates for feline diabetes has not been defined. Recent studies have demonstrated improved glycemic control in healthy and diabetic cats fed low-carbohydrate foods (<15% dry matter) [13–15]. By limiting dietary carbohydrates, blood glucose is maintained primarily from hepatic gluconeogenesis, which releases glucose into the circulation at a slow and steady rate. Fluctuations in blood glucose concentrations related to postprandial glucose absorption are avoided. The metabolic changes associated with feeding low-carbohydrate foods in diabetic cats have not been fully described. The shift in substrate use, from carbohydrates to fats and protein, has been called the "metabolic shift."

The concept of metabolic shift is similar to the concept used in the well-known Atkin's diet [28]. By providing foods extremely low in carbohydrates but with a surfeit of protein and fat, the metabolic drive shifts from glucose oxidation to fat metabolism for the animal's primary energy source. Low-carbohydrate intake results in lower plasma glucose concentrations and limited drive for insulin secretion from the pancreas. Purported benefits of a low-carbohydrate high-protein diet include appetite control, increased calorie loss via futile cycling and ketone loss, improved insulin sensitivity, and a shift from glucose oxidation and lipogenesis to lipolysis and weight loss [28]. Because weight control is vitally important to reversing insulin resistance that occurs in obese diabetic cats, a metabolic shift toward weight loss or weight control is of vital success to the treatment of cats with DM.

Weight control and metabolic shift

The red blood cell, kidney medulla, and central nervous system all have an absolute requirement for preformed glucose from the blood. The typical feline diet provides abundant glucose to meet essential needs. Once this "essential glucose pool" is filled, excess energy supplied as glucose is readily converted to triglycerides and stored as fat in adipocytes. When a high-carbohydrate

diet is consumed, blood glucose rises, insulin requirements are increased, lipoprotein lipase activity increases, and a greater portion of glucose enters the adipose cells, where it is converted to fatty acids and stored as fat. Conversely, when fed a low-carbohydrate food, blood glucose and insulin levels are low and storage of fat becomes more difficult. This metabolic shift from fat storage (lipogenesis) to fat loss (lipolysis) is attributable to several alterations in substrate and hormone availability. With low-carbohydrate intake, the conversion of glucose to α-glycerol phosphate (α-GP) in the adipocytes is reduced. Because α-GP is required for triglyceride formation, lipogenesis is limited. More importantly, low insulin concentrations, together with relative increases in glucagon (in response to amino acid intake), increase cyclic adenosine monophosphate (cAMP) in the adipose cells. High intracellular cAMP activates hormone-sensitive lipase (HSL), the enzyme responsible for lipolysis. Subsequently, within the adipocytes, the rate of triglyceride hydrolysis to free fatty acids (FFAs) increases. FFAs are released into blood bound to albumin (nonesterified fatty acids [NEFAs]), where they serve as a preferred energy source to other tissues. In the liver, NEFAs readily undergo β-oxidation and production of ketone bodies. The muscles, heart, and, to some extent, central nervous system use ketones and NEFAs in preference to glucose.

Simply stated, when lipids and proteins are consumed in the absence of carbohydrates, insulin levels remain low. The metabolic response is similar to that observed during starvation. These signals alter enzyme activities in the intermediary pathways to conserve glucose, limit gluconeogenesis from amino acids (to conserve body proteins), and mobilize fats.

Markers of metabolic shift

The hallmark of effective metabolic shift is increased ketone body (acetoacetate, acetone, and β-hydroxybutyrate [BHBA]) production as measured in the blood and urine. Increased fat metabolism in cats favors the production of BHBA and lesser increases in acetoacetate or acetone compared with human beings, in whom ketogenesis generates high levels of acetoacetate and acetone. Recall that urine reagent strips designed to detect ketones react only with acetoacetate and acetone. Thus, these urine strips are not useful for monitoring benign dietary ketosis in cats, as in people. Only when ketone concentrations are significantly elevated (as in uncontrolled DM) does urine test positive for ketones in the cat.

Ketosis that occurs during low-carbohydrate feeding is relatively mild compared with ketosis that accompanies uncontrolled DM, pregnancy toxemia of ewes, or ketosis of lactating cattle. Levels of BHBA increase from approximately 0.1 mmol/L in the fed state to upward of 3.0 mmol/L when feeding a low-carbohydrate food (W. Schoenherr, Hill's Pet Nutrition, Inc., unpublished data, 2004). At these levels, metabolic complications associated with ketosis are not observed. This is in contrast to DM, where BHBA levels typically exceed 15 mmol/L and are associated with metabolic acidosis and electrolyte imbalances.

What is the evidence for improved glucose regulation by feeding low-carbohydrate foods to diabetic cats? Three studies published over the past 5 years

support the use of low-carbohydrate foods for the management of feline DM. When feeding extremely low-carbohydrate canned foods with or without acarbose (α-amylase inhibitor), blood glucose and serum fructosamine concentrations and exogenous insulin requirements were observed to decline [13]. More interestingly, Mazzaferro and colleagues [13] reported that more than 60% of cats fed low-carbohydrate foods reverted to a nondiabetic state. The proposed mechanism of diabetes reversal is improved glycemic control, lowered insulin requirements, and reversal of sustained hyperglycemia, thereby reversing glucotoxicity and allowing recovery of peripheral insulin sensitivity. Weight control and subsequent improved insulin sensitivity are critical components of the success of low-carbohydrate foods. Newer studies comparing low-carbohydrate foods with a high-fiber high-carbohydrate food in cats with naturally occurring DM also found that a large proportion of cats reverted to a non–insulin-dependent state within 4 months of diet change [15]. Approximately 68% of cats in the low-carbohydrate group and 41% of cats fed high-fiber foods were able to discontinue insulin. Calculated odds ratios indicate that cats fed a low-carbohydrate food are three times more likely to discontinue insulin and revert to a nondiabetic state. For cats that required ongoing exogenous insulin therapy, glycemic control and insulin dose were not significantly different between groups. The responders (improved glucose control and clinical signs) and nonresponders were evident in both food groups but with no clear biochemical or physical markers identified as response predictors.

Is there a "best" carbohydrate source? Carbohydrates sources suggested to have a lower glycemic index in the cat include corn, sorghum, oats, and barley. Highly processed rice (finely ground and fully gelatinized by cooking) is 100% digestible and readily absorbed in cats [29]. Fructose has been labeled a "good sugar" in people with DM. The advantage to people is a low glycemic index relative to other simple sugars. The use of fructose in foods for cats with DM should be avoided. Cats seem to lack hepatic fructokinase activity, which leads to fructose intolerance and potential renal damage [30]. Fructose is uncommon in commercial cat foods, except in semimoist foods, where the humectants may be in the form of sucrose or high-fructose corn syrup.

Ketosis and low-carbohydrate foods

Low-carbohydrate foods can improve weight loss and increase blood ketone levels. Despite possible concerns over diet-induced ketone production and the development of ketoacidosis, diet-mediated ketosis is minimal compared with that seen with poor diabetic regulation (Table 3). In nonketotic cats, the improved glycemic control and peripheral insulin activity seem to negate any complications that might be associated with the slightly increased ketone production. Based on experience, providing adequate insulin therapy is key to correcting ketosis, and low-carbohydrate foods have not been observed to worsen ketosis.

Fiber

Fiber aids in glycemic control by promoting slow and sustained gastrointestinal absorption of glucose after meals. Some studies have found improved insulin

Table 3
Ketone production in the cat

Metabolic status	β-hydroxybutyrate (mmol/L)
Fed state	0.1
Overnight fast	0.3–0.7
Metabolic shift	1–3
Diabetic ketoacidosis	>15

activity and reduced peripheral insulin resistance after fiber supplementation [31,32]. In cats, support for feeding fiber-supplemented foods comes from clinical experience and a study demonstrating that moderate fiber intake improved glycemic control in diabetic cats [32]. Cats fed fiber-supplemented foods (12% wt/wt cellulose) exhibited lower postprandial serum glucose and mean glucose concentrations compared with cats fed similar foods containing starch [32]. Although several studies in rodents and people indicate that soluble fiber is most desirable, evidence of a clear benefit of soluble over insoluble fiber is lacking in the cat. The soluble fiber may be partially fermented to short-chain fatty acids and then used as energy for enterocytes or absorbed into the blood for use by the animal. Recent studies do suggest that moderate levels of fiber suffice when feeding low-carbohydrate foods (<8%), particularly when of mixed fiber source. Not all cats tolerate fiber-enhanced foods without complications. Increase stool volume, food refusal, constipation, dry skin, and unacceptable begging behavior have been associated with high-fiber foods in some cases.

Although an ideal fiber content and source have not been established, it seems that the inclusion of moderate amounts of mixed fiber (approximately 5%–12% dry matter) aids in glycemic control and weight management of the diabetic cat. Additional studies are needed to define the effect and benefit of fiber further.

Feeding Plan

It is important to emphasize that the efficacy of dietary treatment depends on diet selection, feeding method, daily activity, and use of antidiabetic drugs or insulin. In all cases, large variations in activity or diet may alter glycemic control. Food changes or weight loss may result in the need for an insulin dose adjustment by up to 20%.

Food choice

Both high-fiber low-fat and low-carbohydrate high-protein formulas for the management of diabetes are commercially available. Low-carbohydrate foods are available from each of the major therapeutic food manufacturers (Hill's m/d, Purina DM, and Royal Canin DS 44; see Table 2), along with moderate- to high-fiber alternatives. These are good choices because they are palatable, low in protein, and fortified with vitamins and minerals that may be beneficial in DM. In addition, the products are consistent in formula and calorie content,

allowing for the predictable dietary intake needed for optimal diabetic regulation. For cats reluctant to eat therapeutic foods, several gourmet type and growth formula canned foods are available in the grocery chains and have similarly low-carbohydrate levels. A quick check of the ingredient label indicates that these products contain animal meats, vitamins, minerals, and gums (but no grains or flours). Owners must be cautioned that it is only the canned form of these grocery store brands that is low in carbohydrates and that formulas can vary between flavors; thus, label reading is a must.

Studies are limited as to which food profile (high-fiber versus low-carbohydrate) provides optimal glycemic control. Feeding low-carbohydrate foods clearly increases the reversion rate of clinical diabetes to a non–insulin-dependent state (transient diabetes) by threefold compared with feeding high-fiber foods [15]. Nonetheless, transient diabetes occurs when feeding both food profiles (high-fiber or low-carbohydrate), and diabetic control is not significantly different between foods in cats that remain insulin-dependent [15]. There is individual variability in response to low-carbohydrate versus high-fiber therapeutic foods. Like the response to weight control therapy, there are no obvious clinical or biochemical indicators that predict the optimal food profile for an individual diabetic cat. Current recommendations for newly diagnosed cats are to start with a low-carbohydrate food and good insulin control (typically glargine or lente insulin administered twice daily). Canned food is preferred over dry food because weight regulation seems to be better using a high-moisture product. This practice has resulted in the highest rate of diabetic remission (transient diabetes) in cats to date. Cats that are well regulated on moderate-fiber foods, or when higher protein levels are contraindicated, should continue to be fed the current diet. Cats on chronic insulin therapy were equally well controlled on the low-carbohydrate or higher fiber diet [15].

Until further studies are available, the clinician is left using diet history, personal preference, and individual food trials to determine the best food choice.

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