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NEW STRATEGIES IN THE MANAGEMENT OF FELINE DIABETES MELLITUS

Michael E Herrtage MA BVSc DVSc DVR DVD DSAM DECVIM DECVDI MRCVS
Department of Veterinary Medicine,
University of Cambridge

Incidence

Diabetes mellitus (DM) is the second most common endocrine disorder in cats, with an estimated incidence of 0.5% (1 in 200-250 cats). Its incidence appears to be increasing, probably due to an increase in obesity in the cat population. Several risk factors for DM have been identified: age, obesity, neutering and gender. Age has been identified as the single most important risk factor. Diabetes occurs in a wide age range of cats, but most cats are over 6 years of age when diagnosed. The average age at diagnosis is 10 years and the peak incidence is between 9 and 13 years. Diabetes in young cats is extremely rare. Obesity increases the risk of developing diabetes 3- to 5-fold. Given that the prevalence of obesity in cats between 5 and 11 years old is over 40%, the high prevalence of feline diabetes mellitus is understandable. Neutered cats have nearly twice the risk of developing DM and male cats 1.5 times the risk. Genetics may play a role in some breeds (e.g., Burmese cats in Australia).

Pathophysiology

Diabetes mellitus is classified into insulin-dependent (type 1) and non-insulin dependent (type 2) diabetes mellitus. Type 1 diabetes, resulting from immune-mediated destruction of beta cells, appears to be quite rare in cats. Type 2 diabetes, the most common form of DM in cats, is characterised by variable loss of insulin secretory capacity and insulin resistance. Secondary forms of diabetes can develop with pancreatic destruction from pancreatitis and pancreatic adenocarcinoma.

In diabetic cats, factors such as insulin resistance, deposition of islet amyloid, pancreatitis, and glucose toxicity contribute to loss of pancreatic beta cells. The term "glucose toxicity" is used to describe the situation where beta cells are damaged by chronically high blood glucose concentrations, suppressing insulin secretion. Obesity causes reversible insulin resistance and is a major underlying cause of feline diabetes. Hormones produced by adipose tissue, such as leptin and adiponectin, may have a role in the pathogenesis of obesity and diabetes. Hyperglucagonaemia has been documented to develop in obese cats and may be important in the progression from obesity to diabetes as glucagon increases insulin resistance and may hasten exhaustion of beta cells. Insulin antagonism also develops with conditions such as hyperthyroidism, bacterial infections, and steroid therapy; these can trigger the onset of diabetes or precipitate a ketoacidotic crisis in a previously stable diabetic. Cats are very sensitive to the diabetogenic effect of some hormones, particularly corticosteroids, growth hormone and progestins.

Diagnosis and identification of concurrent problems

In normal cats, the stress response (and epinephrine release) can result in transient hyperglycaemia and glucosuria. A diagnosis of DM in the cat is made on the basis of clinical signs plus persistent fasting hyperglycaemia and glucosuria. Obtaining a urine sample is, therefore, critical to making the diagnosis of diabetes (and to determining whether a urinary tract infection is present). Ketonuria may be seen in more complicated cases of DM.

Concurrent disease and/or a history of administration of an insulin-antagonistic drug (e.g., glucocorticoids) are commonly identified in newly-diagnosed diabetic cats and can interfere with tissue responsiveness to insulin. In general, any concurrent inflammatory, infectious, hormonal or neoplastic disorder has the potential to cause insulin resistance and interfere with the effectiveness of insulin therapy. Some causes of insulin resistance, such as obesity and a history of corticosteroid administration, are readily apparent at the time diabetes is diagnosed. Other causes of insulin resistance, such as pancreatitis, are more "occult" and their discovery may require an extensive diagnostic evaluation. Identification and treatment of concurrent disease plays an integral role in the successful management of the diabetic cat. A thorough history, physical examination and complete diagnostic evaluation should always be done in the newly-diagnosed

diabetic cat. Suggested evaluation includes CBC, biochemistry profile, urinalysis, urine culture, T₄, and thoracic radiographs. Other diagnostic tests to consider in an individual case are fPLI (feline pancreatic lipase immunoreactivity), abdominal ultrasound and/or radiographs, and blood pressure measurement.

Diabetic neuropathy is one of the most common chronic complications of diabetes in cats, with a prevalence of about 10% of insulin-dependent diabetics, but is an uncommon clinical finding in dogs. Clinical signs include hindlimb weakness, decreased jumping ability, plantigrade posture and muscle atrophy. Abnormalities in sensory nerves are not as severe as in motor nerves and the thoracic limbs tend to be affected less severely than the pelvic limbs. Axonal degeneration and demyelination are associated with persistent hyperglycaemia, but the cause of diabetic neuropathy is not known.

Managing non-ketotic diabetes mellitus in cats

The basic objective of therapy is to eliminate the clinical signs of diabetes mellitus while avoiding associated complications, especially hypoglycaemia. Other common complications include weakness, ataxia and a plantigrade stance caused by peripheral neuropathy, poor hair coat from lack of grooming, weight loss, recurring ketosis, and poor glycaemic control secondary to concurrent infection, inflammation, neoplasia or hormonal disorders. Another important treatment goal is to maximize the chances of attaining diabetic remission.

Initial insulin therapy. Insulin glargine (Lantus, Aventis Pharmaceuticals) is a long-acting insulin analog that forms microprecipitates at the site of injection from which small amounts of insulin glargine are slowly released. This synthetic insulin differs from human insulin in that an amino acid is replaced by glycine and two arginines. Glargine (dosed at 0.25 U/kg ideal body weight if the blood glucose at diagnosis is < 20 mmol/l or 0.5 U/kg if the blood glucose at diagnosis exceeds 20; SQ) has become the insulin of choice in cats for most endocrinologists as the highest rate of diabetic "remission" has been shown to occur with use of this insulin preparation (in combination with a low carbohydrate diet). Regardless of the type selected, insulin should be administered BID to cats from the outset of therapy. Remission (i.e. reverting to a non-insulin requiring state) usually occurs within one month of beginning insulin therapy, but can occur as late as 4-5 months. Insulin glargine appears to have a duration of effect ranging from 10 to 16 hours in most diabetic cats. The response of diabetic cats to detemir insulin (Levemir) appears to be very similar to glargine but the pharmacokinetics have not yet been studied in cats and there is no published information on its use. Successful glycaemic control can also be achieved with PZI or lente (Caninsulin) insulin. NPH insulin should be avoided due to its short half-life in cats.

Most insulins are available as 100 units/ml (U-100) preparations. Low-dose U-100 syringes (0.3 or 0.5ml) should be routinely dispensed for cats. Note that insulin glargine cannot be diluted, as dilution alters the pH and, hence, absorption characteristics. Using low-dose syringes to improve dosing accuracy is preferable to diluting any insulin preparation. Although insulin glargine does not require refrigeration, glargine is commonly being used for 6 months (rather than the 28 day maximum on the label directions) with refrigeration. Note that Caninsulin is available only at a concentration of 40 U/ml,

Dietary recommendations. Correction of obesity and minimizing the impact of the diet on postprandial blood glucose concentration are important dietary considerations in diabetic cats. Obesity is common in diabetic cats and results from excessive caloric intake typically associated with free-choice feeding of dry (high carbohydrate) cat foods. Insulin resistance caused by obesity can resolve as obesity is corrected. Following weight reduction, glycaemic control often improves and some diabetic cats revert to a subclinical diabetic state. Unfortunately, correction of obesity is difficult in cats because it requires restriction of daily caloric intake, ideally with some increase in caloric expenditure (i.e., exercise). Although there are several diets specifically formulated for weight reduction in cats, diets that minimize intestinal carbohydrate absorption should be fed to diabetic cats. In a newly diagnosed diabetic cat, a weight reduction program is usually postponed until initial glycaemic control is achieved.

The central theme in studies evaluating the impact of diet on glycaemic control in diabetic cats is

restriction of carbohydrate absorption by the gastrointestinal tract, variously by inhibiting starch digestion (acarbose), inhibiting intestinal glucose absorption (high fibre foods), or decreasing carbohydrate ingestion (low carbohydrate, high protein foods). Recently, interest has focused around the latter strategy. Intuitively, the most effective means to minimize gastrointestinal absorption of carbohydrates in the diabetic cat is to feed diets that contain minimal amounts of carbohydrate. Cats are strict carnivores; they maintain normal blood glucose in large part by making glucose from amino acids, rather than from dietary carbohydrates. The diet of feral cats contains large amounts of protein and fat and very little carbohydrate. Conversely, most commercially available dry cat foods provide the majority of ingested calories as carbohydrate. The two primary dietary choices for diabetic cats are high fibre, moderately-fat restricted diets (e.g., Prescription Diet w/d, Hill's Pet Products) or high protein, low carbohydrate, low fibre-containing diets. It has been observed that high protein diets reduce the insulin requirements of diabetic cats. It has been reported that obese cats (> 28% body fat) had a better response (diabetic remission) to a low carbohydrate, protein-replete diet than did cats with < 28% body fat (improved glycaemic control not remission). Interestingly, obese cats exhibited an increase body weight associated with an increase in lean body mass, despite a decrease in percentage of body fat, over the 4 months of the study. Current practice is that non-obese diabetic cats be fed *ad libitum*. Consumption of numerous small meals throughout the day minimises blood glucose fluctuation and optimises glycaemic control in human diabetics, compared with eating larger, less frequent meals. In cats, this strategy follows the cats' natural feeding pattern of eating 10-20 small meals a day.

Oral hypoglycaemic drugs. Oral hypoglycemic drugs work by stimulating pancreatic insulin secretion (sulphonylureas, meglitinides), enhancing tissue sensitivity to insulin (biguanides, thiazolidinediones) or slowing postprandial intestinal glucose absorption (alpha-glucosidase inhibitors).

The oral sulphonylureas (glipizide and glyburide) have been effective in improving control of glycaemia in approximately 20% of newly-diagnosed diabetic cats. No consistent parameters have been identified which allow the clinician to prospectively determine which cats will respond to glipizide or glyburide therapy. One protocol is to administer glipizide (Glucotrol, Pfizer Inc), 2.5 mg per os BID in conjunction with a meal, to non-ketotic diabetic cats that are relatively healthy on physical examination. If vomiting or icterus have not occurred and hyperglycaemia is still present after 2 weeks of treatment, the glipizide dosage is increased to 5 mg BID. Therapy is continued as long as the cat is stable. If euglycaemia or hypoglycaemia develop, the glipizide dosage may be tapered down or discontinued, and blood glucose concentrations re-evaluated one week later to assess the need for the drug. If hyperglycaemia recurs, the dosage is increased or glipizide is reinitiated, with a reduction in dosage in those cats previously developing hypoglycaemia. Glipizide is discontinued and insulin therapy initiated if clinical signs continue to worsen, the cat becomes ill or develops ketoacidosis, blood glucose concentrations remain greater than 15 mmol/l after one or two months of therapy, or the owners become dissatisfied with the treatment.

Monitoring

During the first 24 hours of therapy, perform spot blood glucose measurements to check for evidence of hypoglycaemia (every 3 - 4 hours for initial 12 - 18 hours). Whenever insulin therapy is initiated or changed, the cat should be allowed to "equilibrate" at home for 3 - 6 days before response to insulin therapy is assessed.

At each recheck, remember that the goals of therapy are resolution of clinical signs and avoidance of adverse clinical sequelae (hypoglycaemia). Therefore, the owner's assessment of thirst and urine production, and an accurate weight measurement are very important. A blood glucose curve (a series of timed measurements of blood glucose, such as every 2 hours for 12 hours) is recommended every 10-14 days until an appropriate insulin dose is achieved and thereafter as necessary for monitoring (usually every 2-4 months).

Cats are more prone than dogs to development of the Somogyi phenomenon (hypoglycaemia-induced glucose counter-regulation), even at conservative doses of insulin. When a cat's blood glucose drops too low, release of catecholamines, glucagon, glucocorticoids, and growth hormone cause a rapid release of glucose into the blood. It is important to be aware of this phenomenon in

order to avoid being tempted to increase the insulin dose, as this would accentuate the problem and eventually cause a hypoglycaemic crisis. Starting diabetic cats on low-dose, twice a day insulin therapy at the time that insulin treatment is initiated is helpful in avoiding the Somogyi phenomenon.

Glucose reagent strips (chemstrip BG) read using a glucose meter are used as only one drop of blood is required for each glucose measurement. Some owners are willing to monitor blood glucose at home, which eliminates the effect of hospital stress on results. Teaching the owner to obtain blood glucose profiles at home (using a lancet device to obtain capillary blood samples from the ear - Microlet Vaculance®) eliminates the effects of hospital stress on glucose profile results. An excellent training resource is the video on the website VeterinaryPartners.com (click on cats, then search diabetes). Monitoring urine glucose is not recommended and insulin dosage adjustments should not be made based on the presence or absence of glucosuria.

Serum fructosamine concentration may be used every 3-4 months in lieu of serial glucose profiles as long as history, clinical signs, and random blood glucose measurements also suggest good glycaemic control. Fructosamines are glycated proteins found in blood. They result from an irreversible, nonenzymatic, insulin-independent binding of glucose to serum proteins. They reflect the mean blood glucose concentration over the circulating life span of the protein (2-3 weeks).

One important factor that affects monitoring of diabetic cats is the propensity to develop stress-induced hyperglycaemia caused by frequent visits to the veterinary hospital for blood samplings. Once the insulin dose has been stabilized, serial blood glucose curves should be done when there is a perceived need to change insulin therapy. The determination of good versus poor control of glycaemia should be based on the owner's subjective opinion of presence and severity of clinical signs and overall health of their pet, ability of the cat to jump, its grooming behaviour, findings on physical examination, and stability of body weight. Generation of serial blood glucose curves is generally reserved for newly-diagnosed and poorly-controlled diabetic cats. If stress-induced hyperglycaemia is suspected, switch from reliance on serial blood glucose curves generated in the veterinary hospital to a curve generated by the owner in the home environment or monitor sequential serum fructosamine concentrations. Continuous blood glucose monitoring systems are being used in feline patients and hold promise for improving glycaemic control in "brittle" or frustrating diabetics.

Summary

When treating a diabetic cat, the primary goals are to control clinical signs without causing clinical hypoglycaemia and to maximize the chance of achieving diabetic remission. Identification and treatment of concurrent disease plays an integral role in the successful management of the diabetic cat. Concurrent diseases, such as urinary tract infection and pancreatitis, can interfere with tissue responsiveness to insulin, making glycaemic regulation difficult and predisposing to episodes of ketosis. Minimizing the impact of food type and feeding method on postprandial blood glucose concentration and correction of obesity are important dietary considerations in diabetic cats. A low carbohydrate, high protein diet is recommended but should not be given as the sole therapy in an overtly diabetic cat.