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REVIEW

Managing feline diabetes: current perspectives

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Abstract: Diabetes mellitus is a common endocrine disease in cats. While type 2 diabetes is the most common form seen in cats, other underlying causes may contribute to insulin resistance. Guidelines for diagnosis vary and often do not take into account prediabetic cats. The goals of treatment are to maximize the chance of remission, while minimizing the risks of hypoglycemia. This article presents a further overview of current treatment and monitoring recommendations for diabetic cats.

Keywords: diabetes mellitus, glucose tolerance, diabetic remission, gluconeogenesis, feline, cats

Diabetes in cats

The reported prevalence of feline diabetes mellitus (diabetes) varies from 1 in 100 (1%) to 1 in 400 (0.25%) depending on the population studied.[1–5] An American study has reported the prevalence increasing over the past 30 years, from 1 in 1250 (0.08%) in 1970 to 1 in 81 (1.2%) in 1999, though the contribution of increased diagnosis versus increased prevalence is unclear.[5] Increased susceptibility has been reported in Burmese in Australia, New Zealand, and Europe, and Maine Coon, Russian Blue, and Siamese were reported in the USA and Norwegian Forest cats in Europe.[3,4,6–8] Burmese cats in Australia and the UK are four times more likely to develop diabetes, with 1 in 10 cats aged ≥8 years affected.[2–4]

Diabetes is caused by insufficient insulin secretion from pancreatic β cells resulting in persistent hyperglycemia. Current classification in veterinary medicine is based on human diabetes and the mechanism involved in pancreatic β-cell failure. There are four types of diabetes: type 1, type 2, gestational, and other specific types.[9] Type 1 diabetes is characterized by immune-mediated destruction of β cells leading to an absolute insulin deficiency and it is extremely rare in cats.[10,11] Gestational has not been reported in cats but reported in dogs.[12]

Type 2 diabetes is the most common form seen in cats, accounting for ~90% of cases.[13,14] It is characterized by insulin resistance accompanied by failure of β cells to compensate in response to maintain euglycemia.[9] Risk factors include increased age, male gender, obesity, indoor confinement, physical inactivity, breed, and long-acting or repeated steroid or megestrol acetate administration.[1,4,5,15] These factors lead to decreased insulin sensitivity, and increase the demand on β-cells to produce insulin.[16–18]

The key features of type 2 diabetes are reduced insulin sensitivity (insulin resistance) and reduced insulin secretion secondary to β-cell failure. Cats with diabetes are approximately six times less sensitive to insulin than normal cats.[16,19] β Cells in healthy cats are able to respond to changing insulin requirements and produce more insulin when the demand is increased.[20] Factors associated with type 2 diabetes impair the ability to secrete insulin.[21] Mechanisms that impair β cells result in reduced capacity

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to proliferate to meet the increased demand for insulin, impair insulin secretion, decrease insulin gene expression, and eventually lead to uncontrolled β-cell death.[21] Chronic hyperglycemia creates a continuous cycle of progressive loss of insulin secretion.[22–24]

Other specific types of diabetes include all other causes of diabetes. In cats, this can be caused by loss of pancreatic islets from pancreatitis or neoplasia (adenocarcinoma is reported in 8%–19% of euthanased diabetics in US tertiary referral institutions).[10,25] Pancreatitis may be present in up to 60% of diabetic cats based on biochemical and imaging findings.[26–28] In the majority of these cases, pancreatitis alone does not seem to be sufficiently severe to cause diabetes, but it does contribute to β-cell loss and may influence the probability of diabetic remission.[28,29] Other specific types also include marked insulin resistance secondary to hypersomatotrophism (acromegaly) or hyperadrenocorticism (Cushing syndrome).[10,25,30,31] Acromegaly is the most commonly reported form, typically presenting as poorly controlled diabetes, despite the use of insulin doses that would normally be considered adequate.[32]

Diagnosis

The classical clinical signs of diabetes in cats are polyuria, polydipsia, and weight loss. Glycosuria occurs when blood glucose concentration exceeds the capacity of the proximal tubule to reabsorb glucose from the glomerular filtrate (~14–16 mmol/L [250–290 mg/dL]), and the resulting osmotic dieresis leads to polyuria and compensatory polydipsia.[33,34]

Screening and fasting blood glucose concentrations

Diagnosis is made based on blood glucose concentration; however, currently, there is no commonly accepted lower cut point for diabetes in cats, with values of ≥180–288 mg/dL (10–16 mmol/L) reported as diagnostic.[35,36]

Fasted blood glucose concentration in cats is ~3.0–6.5 mmol/L (117 mg/dL) when measured using a portable glucose meter calibrated for feline blood after overnight hospitalization and withholding food for 18–24 hours.[37,38] Screening blood glucose (measured on entry to the consult room) has an upper reported cut point of 166 mg/dL (9.2 mmol/L), showing the potential effect of stress on diagnosis of diabetes in cats.[39] Acute stress can markedly increase glucose concentrations within 5 minutes and may last for 3 hours or longer.[40] Struggling can increase glucose concentration on average by 74 mg/dL (4.1 mmol/L) and up to 195 mg/dL (10.8 mmol/L) within 10 minutes, associated with increased lactate and norepinephrine concentrations.[40] Cats ≥8 years of age with a screening blood glucose >117 mg/dL (6.5 mmol/L) should be admitted and retested 4 hours later, and if not <117 mg/dL (6.5 mmol/L) then should be retested after 24 hours. While there are no longitudinal studies looking at nondiabetic cats with increased blood glucose concentrations, cats in diabetic remission with mildly increased blood glucose concentration (>135 to <162 mg/dL; 7.5 to <9 mmol/L) are at increased risk of becoming diabetic within 9 months.[38] Therefore, identification of possible prediabetes and subclinical diabetes and appropriate intervention are likely useful for delaying or preventing progression to clinical diabetes in cats.

Hyperglycemia and the sick cat

In hospitalized sick cats, it can be unclear whether stress or diabetes is causing an elevated blood glucose concentration. If hyperglycemia (216 mg/dL; >12 mmol/L) persists for longer than 4–6 hours, low-dose insulin therapy (e.g., 0.5–1 U/cat or 0.2 U/kg q 12 hours) should be given. Exogenous insulin lowers blood glucose and helps overcome deleterious effects of hyperglycemia on β-cell function. Glucose concentrations should be monitored closely and insulin adjusted accordingly.

Fructosamine

Fructosamine is produced by a nonenzymatic reaction between glucose and the amino groups of plasma proteins. It is useful to measure glycemic control for cats where home or in-hospital blood glucose monitoring is not possible, though its usefulness to aid diagnosis of diabetes is variable. In cats, fructosamine concentration probably reflects the mean blood glucose concentration for the preceding week, and only changes >33 μmol/L in an individual cat have significance.[41] Fructosamine concentrations can vary widely between individual cats for a given blood glucose concentration. While sensitivity and specificity of fructosamine for differentiating diabetic from nondiabetic cats have been demonstrated at 93% and 86%, respectively, false-positive results (normal cats with high fructosamine levels) and false-negative results (diabetic cats with normal fructosamine levels) do occur.[42,43] Fructosamine should not be relied upon to differentiate stress–hyperglycemia from diabetes when the blood glucose concentration is ≤360 mg/dL (20 mmol/L), because persistent hyperglycemia of this magnitude often does not increase fructosamine above the reference range.[41] Differentiation should be based on serial blood glucose concentrations, and if present, glycosuria and consistent clinical signs.

Treatment and monitoring

The aim of therapy in newly diagnosed diabetic cats is to maximize the chance of remission by strict glycemic control (72 to <180 mg/dL; 4 to <10 mmol/L), while avoiding hypoglycemia. Diabetic remission is defined as persistent euglycemia without the requirement for exogenous insulin or oral hypoglycemic therapy in cats previously requiring treatment to control diabetic signs.[13,38,44] For long-term diabetic cats that do not achieve remission (≥6 months), the aim is to control clinical signs and avoid clinical hypoglycemia. Remission may occur in a small proportion even after 2 years of insulin treatment, if rigorous glycemic control is maintained.

In newly diabetic cats, early effective glycemic control can resolve glucotoxicity before there is permanent loss of sufficient β cells to maintain euglycemia, which increases the probability of remission. A protocol aimed at strict glycemic control within 6 months of diagnosis showed that 84% of cats achieved diabetic remission compared with 35% ($p<0.001$) when strict glycemic control was not instituted for ≥6 months after diagnosis.[45]

Besides early institution of tight glycemic control, factors associated with remission include a low-carbohydrate diet (12% versus 26% of energy from carbohydrate), long-acting insulin (glargine versus PZI or lente), higher age (suggesting possible slower disease progression), lower maximum dose of insulin (mean maximum dose of glargine of 0.4 U/kg versus 0.7 U/kg or <3 U/cat versus >3 U/cat), lower mean blood glucose after treatment with insulin, and lower cholesterol concentrations.[13,44–47] Corticosteroid administration in the 6 months before diagnosis of diabetes is associated with significantly higher remission rates.[45] Peripheral neuropathy at diagnosis is associated with decreased probability of remission. This is likely because diabetic neuropathy presents later in the course of disease, so these cats have been diabetic for longer period of time and have greater β-cell damage.[45]

To maximize the probability of remission, blood glucose concentration is the most useful guide for adjustment of insulin dose. Home blood glucose monitoring is recommended to avoid the effects of stress hyperglycemia, and it should be measured prior to insulin injection, to prevent inadvertent overdosing of insulin when blood glucose concentration is around the normal range. Ideally, normal or near-normal blood glucose concentrations (54–180 mg/dL; 3–10 mmol/L) will be achieved over each 24-hour period, and clinical signs will resolve. Clinical signs themselves are relatively insensitive indicators of glycemic control when glucose concentration is below the renal threshold (252–288 mg/dL; 14–16 mmol/L).

Continuous blood glucose monitoring

Blood glucose concentration is best measured either with a portable glucose meter calibrated for feline blood, and measured from the ear or paw pad, or with a continuous glucose meter which is internally calibrated and has a long sensor life. Continuous blood glucose monitors measure glucose concentration in the interstitial fluid, mostly using an electrochemical sensor attached to a small monitor or transmitter implanted subcutaneously in the flank, lateral thorax, interscapular space, or dorsal neck in cats.[48] The MiniMed Gold (Medtronic), Guardian Real-Time (Medtronic), GlucoDay (Menarini Diagnostics), iPro (Medtronic), and FreeStyle Libre (Abbott) have been reported for use in cats and dogs.[48,49] However, many models still require calibration three times a day with blood glucose measurements obtained by traditional methods, most sensors need replacing every 3–7 days, and the glucose recording range can be limited. The FreeStyle Libre (Abbott) is a newer model that is calibrated in the factory and does not require additional blood glucose measurements to calibrate at home, and the sensor is suitable for 14 days of use.[50]

Continuous glucose monitors are useful for hospitalized patients needing intensive monitoring; however, they are also useful for home use for diabetic cats that are difficult to stabilize as they allow identification of short duration of insulin action and Somogyi events. Guardian Real-Time is useful for hospitalized cats requiring real-time displays for monitoring.[48] For home monitoring, the FreeStyle Libre has several benefits as listed above making it the most suitable choice, though there are some limitations.[49]

Insulin therapy

The most effective treatment for achieving excellent glycemic control is insulin, with several types available for use in cats.[13]

Lente insulin (Caninsulin/Vetsulin)

Lente insulin is an intermediate-acting insulin.[51] Caninsulin or Vetsulin (Merck Animal Health) is a porcine-derived lente insulin licensed for use in cats in many countries. The concentration of 40 U/mL differs from insulin registered for human use and some veterinary-registered insulins, which are 100 U/mL. It is important that the appropriate 40 U/mL syringes are not inadvertently changed for 100 U/mL syringes.

Starting dose for lente insulin is 0.25–0.5 IU/kg body weight, q 12 hours, and should not exceed 3 IU/cat.[52] In a 12-month study of 25 cats (15 newly diagnosed), 84% were considered to have a good or excellent response to treatment,

based on owner satisfaction and resolution of clinical signs, and 28% achieved diabetic remission within 16 weeks of starting treatment.[53] Another study of 46 cats (39 newly diagnosed) showed that good to excellent control was achieved in 72%, based on the resolution of clinical signs, and 15% achieved remission within 20 weeks.[54]

In diabetic cats, nadir blood glucose concentration typically occurs 3–6 hours (mean 4 hours) after insulin administration, and blood glucose concentration returns to preinjection concentrations ranging from 8 to 10 hours after insulin administration (termed return to baseline or duration of action).[54,55] Because of this relatively short duration of lente action, even with twice-daily dosing, hyperglycemia typically occurs for 2–3 hours twice daily prior to each injection, which likely contributes to lower remission rates in cats treated with this insulin.[55,56]

Protamine zinc insulin

Protamine zinc insulin (PZI; ProZinc, Boehringer Ingelheim) is available for use in cats in the US and UK, having been removed from the human market in the 1990s. ProZinc has a concentration of 40 U/mL, and therefore, use of appropriate insulin syringes must be discussed as with lente insulin. While ProZinc is a human recombinant insulin, some compounding pharmacies in the US still provide bovine-origin PZI for veterinary use; however, studies have shown inconsistencies in compounded products.[57]

Initial doses recommended are either 1–3 U/cat (0.22–0.66 units/kg) or 0.25–0.5 units/kg ideal body weight, depending on the severity of clinical signs and hyperglycemia.[13,58] Of the 133 diabetic cats treated with PZI (120 newly diagnosed and 13 previously treated with other insulin), 85% obtained good control within 45 days.[58] In a comparative study of 24 newly diagnosed diabetics, 38% (3/8) of 8 cats treated with PZI achieved remission within 112 days, which was not significantly different to remission rates achieved in 25% (2/8) of cats treated with lente insulin.[13]

Glargine

Glargine (Lantus; 100 U/mL) is a long-acting human insulin analog that is soluble in acidic solutions but forms microprecipitates in the neutral pH of the subcutaneous tissue. These microprecipitates slowly release small amounts of insulin over 24 hours.[59,60] In healthy cats, the duration of action is significantly longer than lente insulin (10 hours, range 5 to >24), though similar to PZI (21 hours, range 9 to >24).[61]

Glargine is used together with a low-carbohydrate diet to minimize prandial increases in blood glucose in cats. Twice-a-day administration is recommended to provide overlap of insulin action from the proceeding injection and increase the probability of remission.[61–63] The starting dose for glargine is 0.25 U/kg of ideal body weight, if blood glucose concentration is <360 mg/dL (<20 mmol/L) or 0.5 U/kg if blood glucose is >360 mg/dL.[13,64] When transitioning to glargine from another insulin, for doses <3 IU direct substitution is usually suitable; however, for doses >3 IU, conservative dosing of half to two-thirds of the dose is recommended, but it will be increased within 48–72 hours if control is not adequate.[65]

Significantly higher remission rates were achieved by 16 weeks of treatment with glargine (8/8 cats), compared with lente insulin (2/8) and PZI (3/8) in newly diagnosed diabetics fed a low-carbohydrate diet (6% of energy from carbohydrate).[13] In 55 diabetic cats, the remission rate was 84% when glargine was started within 6 months of diagnosis using protocol aimed at achieving euglycemia.[45] However, a recent clinical trial of 46 cats found that while a higher percentage of cats receiving glargine went into remission compared with those treated with PZI (33.3%versus 23%), this was not significantly different.[66]

Detemir

Detemir (Levemir, NovoNordisk) is a long-acting human insulin analog (100 μ/mL). While once-a-day dosing is adequate for humans, the duration of action in healthy cats is shorter and twice-daily dosing is recommended.[62] Initial doses for detemir are similar to glargine, with 0.5 units/kg if blood glucose concentration is >360 mg/dL (20 mmol/L) and 0.25 units/kg if <360 mg/dL.[64] Cats may require ~25%–30% lower maximum dose of detemir than glargine initially.[45] Cats can exhibit an initial increased sensitivity to detemir for 24–48 hours; thus, if changing from glargine or other insulin, start with about half the dose of glargine and increase dose within 48 hours if insufficient glucose lowering occurs. Home monitoring is recommended because preinsulin blood glucose concentrations vary daily. Increase dose based on the same dosing protocol as glargine.[64,65]

Of the 11 cats treated with detemir within 6 months of diagnosis and a protocol aimed at euglycemia, 81% went into remission, whereas only 42% of 6 cats that had been diabetic for longer than 6 months achieved remission, findings similar to glargine-treated cats.[67]

Degludec

Degludec (Tresiba, NovoNordisk) is an ultralong-acting insulin with a longer half-life. Due to its slow release, there is no peak in activity, and it is less likely to result in hypoglycemia.[68] Its use has not been reported in cats.

Choosing an insulin

Given the high rates of diabetic remission in recent studies using long-acting insulin, low-carbohydrate diets, and protocols aimed at achieving normal or near-normal blood glucose concentrations, insulin should be chosen to maximize the probability of diabetic remission. Glargine and detemir are the only insulins reportedly associated with remission rates of >80% in newly diagnosed cats when combined with a low-carbohydrate diet, and hence, these should be the first choice when choosing insulin for a newly diagnosed diabetic cat.[13,67] However, neither is registered for use in cats, and in some countries (e.g., the UK), laws may require the use of a veterinary-approved product first. Because the highest remission rates occur in cats that are managed with a protocol aimed at achieving euglycemia within 6 months of diagnosis, the requirement to treat with another insulin first may reduce the probability of remission.

Diet

Cats are obligate carnivores, with diets of feral cats eating natural prey having a mean daily energy intake of ~2% carbohydrate (nitrogen-free extract), 52% crude protein, and 46% crude fat.[69] However, commercial feline dry food diets have up to 60% of their energy from carbohydrates (mean 41%).[5,70,71] Compared with dogs and humans, cats have a reduced capacity to metabolize a high glucose load, resulting in higher blood glucose concentrations after a carbohydrate load, and have an extended postprandial period of 8–15 hours compared with 2–3 hours for humans and 3–6 hours for dogs.[9,72,73] While cats do exhibit some metabolic flexibility in dealing with dietary carbohydrates provided minimum protein requirements are met, glucose metabolism in cats is unique, resulting in a relative carbohydrate intolerance, as the gluconeogenic pathway is almost always permanently "switched on".[74,75] Delayed gastric emptying, reduced small intestinal disaccharidase activity, and reduced and delayed insulin secretion likely contribute to longer postprandial increase in blood glucose concentrations following a high carbohydrate load.[73,76,77]

Obesity is the most important acquired risk factor for diabetes, as overweight cats have 4.6 times greater risk of diabetes than cats in ideal body condition.[4,16,35] Approximately 20% of obese cats >8 years of age are prediabetic with impaired glucose tolerance or impaired fasting glucose.[37,78,79]

Low-carbohydrate diets (≤12% metabolizable energy [ME]) are indicated for cats at increased risk of diabetes, such as senior age, susceptible breed, and concurrent medications. Older cats with other risk factors for diabetes such as European or Australian Burmese and cats receiving repeated corticosteroid injections would likely benefit from a low-carbohydrate diet to minimize the insulin secretion required to maintain euglycemia.[80]

The highest remission rates in diabetic cats (>80%) are reported using a very low-carbohydrate diet (<6% ME) in combination with protocols aimed at achieving normal or near-normal blood glucose concentrations.[13,67] However, the relative contribution of diet in increasing the probability of remission is unknown.

Controlled weight loss via energy restriction is important to normalize the body condition and muscle mass in obese diabetic cats.[80] A suitable weight loss diet for a diabetic cat is fat <4 g/100 kcal, carbohydrates <3 g/100 kcal, and protein >10 g/kcal.[80] Increasing the proportion of wet food helps to decrease energy intake and body weight as moisture increases food volume and hydration.[81] While not many cats achieve remission before reaching ideal body condition, maintaining ideal body condition is likely important for maintaining remission.

Oral hypoglycemics

Oral hypoglycemics may be used in human type 2 diabetes patients with sufficient endogenous insulin secretion to maintain euglycemia without insulin therapy. Sulfonylureas and meglitinides stimulate insulin secretion from pancreatic β cells.[82,83] However, the majority of diabetic cats have insufficient β-cell function to achieve good glycemic control using these alone.[30,84] Similarly, biguanides such as metformin require functional β cells and sufficient circulating insulin to be present if they are the sole therapy.[85] In five newly diagnosed diabetic cats treated solely with metformin, only one cat had measurable serum insulin concentration pretreatment, and this was the only cat that achieved good glycemic control.[86] While α-glucosidase inhibitors such as acarbose can slow intestinal glucose absorption and reduce peak postprandial glucose concentrations, they are minimally effective in cats eating multiple small meals.[85,87] The trace element vanadium supplemented at 45 mg/cat/day improved glycemic control in diabetics treated with PZI insulin, with a mean insulin requirement of 3 U in vanadium-supplemented cats compared with 5 U in cats treated with PZI alone.[88]

Insulin treatment is associated with a higher probability of achieving glycemic control and eventual diabetic remission, compared to the sole use of oral hypoglycemic agents, and this continues to be the recommended treatment for diabetic cats.

New and emerging therapies

Incretins are gastrointestinal hormones released in response to food intake that stimulate the release of insulin and include glucagon-like peptide 1 (GLP-1) agonists and dipeptidylpeptidase-4 inhibitors.[89] In humans with type 2 diabetes, exenatide (twice daily) and extended-release extenatide (once weekly) are injectable GLP-1 agonist preparations used as an adjunctive or sole therapy. In newly diagnosed diabetic cats treated with glargine and a low-carbohydrate diet, 15 cats also treated with extended-release exenatide had improved glycemic control and remission rates compared with 15 cats that received a placebo, though this was not significant.[90] Further studies are required to investigate their cost-effectiveness in diabetic cats.

Diabetic remission

Diabetic remission is the ideal outcome of treatment. However, ~25%–30% of diabetic cats in remission will relapse and require insulin treatment to be recommenced.[38,44,46] The majority of cats that relapse do not achieve a second remission, although in one study of nine cats that relapsed, two achieved a second remission.[45] Most diabetic cats in remission do not have normal β-cell function or sufficient insulin secretion to maintain normal glucose tolerance when challenged with an intravenous (IV) glucose tolerance test (GTT) and should be considered prediabetic. Approximately 76% have impaired glucose tolerance evident after a glucose challenge and 19% have impaired fasting glucose concentrations (mild persistent hyperglycemia >117 to <180 mg/dL; >6.5 to <10 mmol/L).[38] Monitoring with GTTs can identify cats at risk of relapsing. Fasting blood glucose of ≥135 mg/dL (≥7.5 mmol/L), severely impaired glucose tolerance (≥5 hours return to ≤117 mg/dL or ≤6.5 mmol/L after a 1 g/kg glucose IV), and a blood glucose concentration during a GTT of >252 mg/dL (>14 mmol/L) at 3 hours were all significantly associated with a relapse within 9 months of achieving remission.[38]

Home blood glucose monitoring and GTTs should be used to detect those cats at greater risk of relapsing. Cats with persistent blood glucose concentrations >117 mg/dL (6.5 mmol/L) require management with low-carbohydrate diets and weight loss, if appropriate.[91] Oral hypoglycemics, incretin-based therapies, or low-dose insulin therapy may have a role in managing cats with impaired glucose tolerance or fasting blood glucose to reduce the risk of relapse; however, further investigation is required.

Poorly controlled diabetic cats

Some diabetic cats will prove difficult to control, often requiring high doses of insulin administration. This may be due to owner noncompliance, insulin choice, inappropriate dosing, or underlying diseases contributing to insulin resistance.

Inappropriate storage of insulin leading to loss of potency, incorrect administration (e.g., poor injection technique and drawing up air bubbles), and irregular dosing can all contribute to poorly controlled diabetes and should be ruled out as much as possible by discussing with the client and watching their injection technique. Dosing errors occur when one type of syringe is changed for another without proper education. Porcine lente insulin (40 U/mL, Vetsulin/Caninsulin, Intervet) and Prozinc use 40 U/mL syringes (1 gradation=0.025 mL), whereas other insulins use 0.3 mL, 100 U/mL syringes (1 gradation=0.01mL). Duration of action of intermediate-acting insulins (e.g., lente) may not be sufficient with twice-daily dosing to maintain a prolonged decrease in blood glucose concentrations.[55,61] In these cats, a change to longer acting insulin such as glargine or detemir typically resolves the poor control.

Underlying diseases can contribute to insulin resistance and poor control, despite good client compliance and appropriate insulin selection and dosing. Further testing should be offered if insulin doses exceed 1.0–1.5 IU/kg q 12 hours, and blood glucose control remains poor (mean blood glucose >270 mg/dL or 15 mmol/L).

Acromegaly, or hypersomatotropism, results from increased production of growth hormone, typically due to a pituitary adenoma, and accounts for 25%–30% or more of cases with poorly controlled diabetes. It is the most common underlying disease in cats with poor diabetic control.[92] Secretion of insulin-like growth factor-1 (IGF-1) is also increased, which mediates the anabolic changes associated with the disease, although many cats with acromegaly will have a normal appearance.[32] Clinical signs include polyuria, polydipsia, polyphagia, and weight gain.

On average, acromegalic cats require insulin doses more than twice those required in nonacromegalic diabetics, though a small minority will initially have good glycemic control and may even achieve remission. Median insulin doses reported are 7 IU twice a day (range 1–35 IU), though sometimes extreme doses are required that would be fatal in other cats (20 to >70 IU).[32,92]

The most commonly used diagnostic test for acromegaly is IGF-1 testing, with concentrations typically increased >1000 mg/mL in acromegalic cats. It is recommended that IGF-1 testing be delayed until 6–8 weeks after insulin therapy is started, as insulinopenia present at the time of diabetic diagnosis may result in a falsely low concentration.[32] Intracranial imaging with magnetic resonance imaging or computed tomography is useful to confirm diagnosis.

Treatment options include palliation with insulin, surgery, radiation, and medical management. Surgery and radiation are limited in their geographical availability, so palliation with high insulin doses accompanied by home blood glucose monitoring is the most common method used.

Hyperadrenocorticism is a less common cause of insulin resistance compared with acromegaly and rarely requires similarly high insulin doses.[32] At diagnosis, ~80% of cats with hyperadrenocorticism are diabetic.[93] Excessive endogenous glucocorticoid, associated with either a function tumor of the pituitary gland or the adrenal cortex, is associated with impaired insulin sensitivity and decreased insulin secretion from pancreatic β cells.[32] Clinical signs include polyphagia, polyuria, polydipsia, weight loss, pot-bellied appearance, hepatomegaly, and skin fragility.[94] A low-dose dexamethasone suppression test using 0.1 mg/kg dexamethasone IV is commonly used for diagnosis.

Pancreatitis is present at the time of diagnosis in 60% of diabetic cats based on biochemical and imaging findings, though few have clinical signs.[10,28] Diabetic remission can be achieved in cats diagnosed with acute pancreatitis at the time of diagnosis of diabetes, and some may return to normal glucose tolerance with resolution of their disease.[27] Home blood glucose monitoring and appropriate adjustment of insulin dose are recommended to maintain glycemic control and maximize the probability of remission.

Hyperthyroidism has been associated with impaired glucose tolerance; however, it does not appear to cause clinically appreciable insulin resistance in most diabetic cats.[95]

Bacterial infection has been associated with decreased glucose tolerance, insulin resistance, and hyperinsulinemia in humans and dogs.[96,97] Approximately 12%–13% of diabetic cats have urinary tract infections because of increased risk associated with glucosuria and decreased urine concentration.[98,99] The most common urinary pathogen identified in diabetic cats is *Escherichia coli*.[99] Fungal urinary tract infections, such as *Candida albicans* or *Candida glabrata*, have also been reported in cats.[100,101] All cats with high insulin requirements and poor control should have a thorough workup, including urine sediment exam, and appropriate treatment for any infections identified.

Renal disease

Diabetic nephropathy is diagnosed in 20%–40% of diabetic humans. Though not routinely recognized in diabetic cats, chronic kidney disease (CKD) (common in older cats) is reported in 26%–62% of diabetic cats.[45,67,102] Tubulointerstitial nephritis is the most common histological finding in cats with renal disease; however, in a study of six diabetic cats, 50% had glomerular changes compatible with those seen in human diabetic nephropathy.[103,104] Microalbuminemia and urine protein/creatinine ratio (using a 0.4 cutoff) have been demonstrated to be significantly higher in diabetic cats compared with healthy control cats.[102,105]

Controlled amounts of protein and restricted phosphorus improve the survival time in cats with chronic renal disease, and therefore, high-protein and low-carbohydrate diabetes diets recommended to manage diabetes are likely contraindicated, especially in cats with IRIS stages 2 or 3 of CKD.[106]

Hypoglycemia

A potential complication of insulin treatment is hypoglycemia, manifesting as either biochemical (or asymptomatic) hypoglycemia or clinical (symptomatic) hypoglycemia. Severe hypoglycemia (≤18 mg/dL or 1 mmol/L*)* is potentially life threatening as the brain requires a continual supply of glucose diffusing from the blood.[107] Excessive insulin rapidly transports glucose into peripheral insulin-sensitive tissues, so insufficient glucose is left to adequately supply the brain.[108]

Clinical signs, if they occur (clinical hypoglycemia), include lethargy, depression, ataxia, seizures, or, in severe cases, coma. In cats, cutoffs for biochemical hypoglycemia in clinical insulin trials have been reported as <54 mg/dL or 3 mmol/L measured with a meter calibrated for whole human blood.[13,45] In 28 cats fasted and hospitalized overnight, the lower 95% CI for normal blood glucose concentration was 41 mg/dL (2.3 mmol/L) measured with a meter calibrated for feline blood.[38]

Overadministration of insulin (iatrogenic hypoglycemia) may be caused by client error in drawing up the dose, or may follow an increase in the insulin dose or be associated with the recovery of endogenous insulin secretion.[13] Insulin doses should be adjusted to meet the decreased insulin requirements in cats approaching diabetic remission; otherwise, hypoglycemia is likely. Overdose can occur when a 40 U/mL syringe (1 gradation =0.025 mL) is inadvertently substituted for a 0.3 mL, 100 U/mL syringe (1 gradation =0.01 mL) and can be life threatening.

Biochemical hypoglycemia is managed by feeding the cat, preferably a high-carbohydrate meal (>35% of energy from carbohydrate) and glucose containing solution (e.g., honey and glucose syrup) if mild clinical signs occur. Insulin administration should be stopped until hyperglycemia occurs (>117 mg/dL; 6.5 mmol/L or >216 mg/dL;12 mmol/L), then the dose should be reduced by 25%–50%.[87,109]

Severe clinical hypoglycemia (marked ataxia, seizures, and coma) is an emergency situation and requires hospital

admission. Prior to transport, owners can administer a concentrated glucose solution either orally or via the rectum using a Vaseline-lubricated syringe without a needle.[107] Once hospitalized, treatment typically consists of an initial IV glucose bolus (0.5 g/kg) and a continuous infusion of 2.5% until normal blood glucose concentration can be maintained.[107,110]

Rapid compensation for hypoglycemia in the body normally occurs by decreasing insulin production and stimulating glucagon from the pancreas and epinephrine from the adrenal medullae.[111] However, glucagon's production by pancreatic α cells in response to hypoglycemia is absent or diminished in diabetics.[112] Glucagon injection kits are used to stimulate hepatic gluconeogenesis and glycolysis to increase blood glucose concentration in human diabetics with severe hypoglycemia.[111] In hypoglycemic dogs, glucagon continuous rate infusion (initial rate 5 ng/kg/min) was used for the treatment of refractory seizures in a dog with insulinoma and 9 dogs with insulinoma, paraneoplastic hypoglycemia, and diabetic hypoglycemia (bolus and initial rate of 10–15 ng/kg/min).[113,114] Glucagon bolus markedly improved neurologic signs in a diabetic cat, which had persisted after euglycemia had been restored by dextrose infusion.[113] No adverse effects were noted. Glucagon is initially given as a bolus of 50 ng/kg and then administered at a rate of 10–15 ng/kg/min, but may need to be increased up to 40 ng/kg/min to maintain euglycemia.

Disclosure

The authors report no conflicts of interest in this work.

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