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ISSUES IN ENDOCRINOLOGY

Managing Feline Diabetes Mellitus

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Diabetes mellitus (DM) is a common endocrinopathy in cats, with reported prevalence rates ranging from 0.4% to 1.2%.[1-4] The vast majority of cats with experimentally induced diabetes developed an initial period of insulin resistance, with the associated persistent hyperglycemia directly reducing functional pancreatic beta cell mass.[5] Though an oversimplified explanation, this "glucotoxicity," paired with damage stemming from progressive islet amyloid deposition, generation of reactive oxygen species, and local inflammation, leads to permanent insulin dependence if left uncorrected.[6] Factors related to the patient's diet and adiposity and the presence of comorbid conditions (e.g., acromegaly, pancreatitis) likely contribute to the pathogenesis of feline DM as well as influence response to therapy and chances for achieving remission.

DIAGNOSIS

Overt DM is diagnosed by documenting persistent hyperglycemia with glycosuria in a patient with appropriate clinical signs (polyphagia, polydipsia, polyuria, and/or weight loss).[7] To rule out stress hyperglycemia, additional testing such as blood or urinary glucose monitoring in a nonstressful environment or assessing a serum fructosamine concentration to gauge mean blood glucose (BG) over the preceding 1 to 2 weeks may be required.[8] Some cats may present with a plantigrade stance from diabetic neuropathy (**FIGURE 1**).

A "preclinical" diabetic state is likely to exist in cats before the onset of overt DM, similar to the

FIGURE 1. Cat with plantigrade stance caused by diabetic neuropathy.

EXCESSIVE THIRST
Owner-reported clinical signs, such as polydipsia, often reflect the patient's true state of glycemic control better than most biochemical analyses.

pathogenesis in people. During this time, modest or intermittent hyperglycemia suggesting glucose intolerance may contribute to only mild clinical signs that go unrecognized by the owner. While no standardized method currently exists to identify these prediabetic patients, the finding of repeated mild hyperglycemia on routine diagnostic screenings of a healthy patient should not always be written off to stress. Serial glucose monitoring, fructosamine assessment, or a glucose tolerance test may be warranted if a prediabetic state is suspected.

MANAGEMENT

The general goals of treatment are to mitigate clinical signs through improvement of hyperglycemia and

Potential Complements or Future Alternatives to Insulin Therapy

Glucagon-like peptide 1 (GLP-1) analogues have received attention as a possible alternative or complement to insulin therapy. While still injectable, these products would allow a reduction in the frequency of injections to once weekly instead of once to twice daily. The GLP-1 analogue exenatide-ER (Bydureon, AstraZeneca) was evaluated in a population of 30 diabetic cats concurrently treated with glargine insulin and dietary modification.[1] The drug was proven safe; however, diabetic control and remission outcomes were not statistically different from placebo. Larger studies are warranted to determine if GLP-1 analogue use provides any advantage over standard management protocols.

Oral hypoglycemics, such as the sulfonylurea glipizide, have historically been reserved only for patients in which insulin therapy is vehemently declined or cannot be administered by the owner.[2] The authors do not recommend using glipizide, as the medication is only temporarily effective in some cats in combination with dietary modification and delays appropriate treatment with insulin, thereby possibly predisposing patients to diabetic complications.[3] Novel oral hypoglycemic therapies, such as renal sodium-glucose linked transporter 2 (SGLT2) inhibitors, which induce urinary glucose wasting, may provide future alternatives to insulin injections for management of feline DM, but prospective studies are needed.

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avoidance of diabetic complications (e.g., hypoglycemia, ketosis). These goals are most reliably met using a combination of insulin administration and carbohydrate-restricted dietary modification. A subset of newly diagnosed or insulin-naïve cats in which DM is quickly well controlled may go on to achieve diabetic remission, loosely defined as normoglycemia independent of insulin therapy for more than 4 weeks.[9]

Reported remission rates range from 0% to 100% using various insulin or dietary protocols.[9-11] A survey of 282 cats managed by diplomates of the American Board of Veterinary Practitioners across the United States reported remission rates of 8% to 42% with an average rate of 26% for all cats evaluated.[12] The authors feel this average rate is a realistic figure to discuss with owners in regard to the likelihood of a newly diagnosed diabetic cat achieving remission. Approximately 30% of cats that achieve remission relapse, so maintenance of an appropriate diet and diligent monitoring for recurrence of clinical signs of diabetes are worthwhile.[13]

Insulin Therapy

Most available insulin preparations (**TABLE 1**) contain human insulin or insulin analogues engineered through recombinant DNA technology using bacteria or yeast; the exception is porcine zinc insulin suspension. Most preparations use amino acid modifications to the insulin molecule and/or added zinc or protamine for the purpose of slowing absorption and/or increasing the duration of insulin action. The authors recommend either protamine zinc insulin (PZI) or glargine as first-choice insulin selection and initiation of all insulin preparations at a starting dose of 1 to 2 units per cat, given subcutaneously twice daily.[7,21]

Unlike dogs, most cats do not experience a profound postprandial hyperglycemia.[22] So while meal feeding immediately before insulin injection is ideal, diabetic cats can "graze" over the course of the day if necessary. Owners should monitor for any cessation of food or water intake, as well as signs of gastrointestinal upset (i.e., vomiting or diarrhea), which may require a temporary insulin dose reduction to prevent inadvertent hypoglycemia.

Assessment of glycemic response immediately after starting insulin is not recommended; instead, assessment is typically delayed until 7 to 14 days after treatment initiation. However, spot-checking a glucose reading daily after starting insulin therapy to identify lower than

desired glucose values (typically <100 mg/dL), which might prompt a dose reduction, would be acceptable.

Dietary Therapy

The goals of dietary therapy are to complement insulin in controlling hyperglycemia through limiting carbohydrate availability as well as to assist in achieving or maintaining an ideal body weight (BW). Diets containing a high-protein (≥40% metabolizable energy), low-carbohydrate (≤12% metabolizable energy) nutrient profile are preferred.[23-25] Obese cats should be fed a total daily caloric requirement calculated using their ideal BW, with regular monitoring to ensure gradual (<2% BW reduction per week) weight loss.[7] Achieving effective control of hyperglycemia with a combination of glargine insulin and dietary therapy within 6 months of the initial DM diagnosis increases diabetic remission potential.[24]

MONITORING

No gold-standard diagnostic exists for monitoring diabetic patients or directing therapeutic decision-

TABLE 1 Commercially Available Insulin Products

INSULIN	BRAND NAME (MANUFACTURER)	CONCENTRATION (U/ML)	FDA APPROVED FOR CATS?	MECHANISM OF PROLONGED DURATION	NOTES
Protamine zinc insulin (PZI)[14,15]	ProZinc (Boehringer Ingelheim)	U40	Yes	Added protamine sulfate and zinc oxide components promote crystallization in tissues.	—
Glargine[16]	Lantus (Sanofi)	U100	No	Amino acid alterations promote solubility at an acidic pH of 4.0 (in vial) and precipitation around a physiologic pH of 7.0. This tissue precipitation delays absorption and extends the duration of insulin action.	As pH plays an essential role in the action of glargine, glargine should never be diluted without using the proper diluent to prevent action interference.
	Basaglar (Eli Lilly & Boehringer Ingelheim)	U100			
	Toujeo (Sanofi)	U300			
Detemir[17,18]	Levemir (Novo Nordisk)	U100	No	A fatty acid added to insulin's molecular structure enables strong but reversible binding to albumin, which slows absorption and extends the duration of action.	Detemir has a higher molar concentration of insulin than other preparations, which can increase the hypoglycemic effect in some species, such as dogs, potentially requiring lower starting doses. Cats do not appear to be as susceptible to this concentration difference.
Porcine zinc[19]	Vetsulin and Caninsulin (Merck Animal Health)	U40	Yes	The amorphous and crystalline zinc insulin content is manipulated.	The currently available product has unique handling instructions.
Degludec[15]	Tresiba (Novo Nordisk)	U100	No	A single amino acid substitution causes multi-hexamers to form in the subcutaneous tissues, delaying insulin absorption.	—
Neutral protamine Hagedorn (NPH)[20,a]	Humulin-N (Eli Lilly)	U100	No	Added protamine sulfate and zinc oxide or chloride components promote crystallization in tissues.	—
	Novolin-N & ReliOn-N (Novo Nordisk)	U100			

*a*NPH insulin formulations are not currently recommended in cats due to their inconsistent effect and short duration of action.[20] The authors typically reserve them only for rare circumstances when all other insulin options have failed to control the cat's DM.

Most patients with clinically well-controlled diabetes (serum glucose between 100 and 300 mg/dL over the course of the day) are expected to have glucosuria.

It should be determined at each visit whether the owner has noted signs of hypoglycemia (weakness, lethargy, tremors, collapse episodes, and/or seizures). Persistence of signs at home suggests the patient is unregulated, but the presence of these abnormalities does not provide insight as to the source of the glycemic dysregulation (i.e., excessive or insufficient insulin dose or inappropriate duration of action). Therefore, persistent clinical signs should be a catalyst for an assessment of the patient's insulin response before making changes to insulin therapy.

making. Additionally, management decisions are complicated by factors unique to veterinary medicine, such as owner compliance and finances and patient stress hyperglycemia. In the authors' opinion, individualizing a monitoring plan for each patient using a combination of owner-reported clinical signs and biochemical data maximizes the accuracy of assessments used to direct treatment recommendations.

Most diabetic monitoring tools are used to gauge the general level of glycemic regulation. These tests alert the veterinarian that DM control is present or absent; however, they should not be used alone in directing changes to insulin therapy. Ideally, cats with abnormal monitoring results should have their insulin response evaluated through the generation of a BG curve.

Owner-Reported Clinical Signs

Clinical signs reported by the owner have been shown to provide information that often reflects the patient's true state of glycemic control better than most biochemical analyses.[26] Clinical signs of DM are most pronounced when the BG concentration is above the renal threshold for reabsorption (~250-300 mg/dL). When concentrations are above this threshold, glucose spills into the urine, creating an osmotic gradient that pulls in excess body water. This contributes to the development of an obligatory polyuria that stimulates a compensatory polydipsia in an attempt to maintain adequate hydration. Additionally, when the insulin concentration is insufficient, nutrient uptake by tissues is impaired and insulin does not function in its physiologic role as a central regulator of satiety. Therefore, client-provided information about the presence or absence of polyuria, polydipsia, polyphagia, and weight loss is an essential component of each diabetic evaluation.

Serial Evaluation of Body Weight

An accurate BW should be recorded at each patient evaluation. Ideally, the BW would be obtained in a similar fashion (i.e., timing following meals, urination, or defecation) and on the same scale to maximize the accuracy of observed trends. Fluctuations in BW can provide useful insight into the patient's relative state of glycemic regulation, with weight gain suggesting glycemic control and unexpected weight loss suggesting unregulated DM.

Changes in BW need to be considered along with additional systemic factors such as the patient's daily caloric intake, active attempts at weight loss, and/or concurrent disease processes (e.g., hyperthyroidism or renal disease). An unintentional downward trend in BW should prompt further assessment of the patient's insulin response, especially when clinical signs are present. Weight gain in the face of otherwise poor clinical DM control may suggest the presence of acromegaly, especially if consistent clinical findings are present (e.g., organomegaly, changes to facial features).

Glycosylated Serum Proteins

Proteins in the bloodstream normally undergo nonenzymatic and permanent binding reactions with circulating carbohydrates. Therefore, glycosylated serum proteins are expected during euglycemia and established reference ranges exist for cats.

Fructosamine is the most commonly used glycosylated serum protein test, with normal concentrations in cats reported between approximately 150 to 350 μmol/L.[27] Serum fructosamine concentration has been correlated with the mean BG concentration during the 1 to 2 weeks before measurement.[28] An elevated serum fructosamine concentration suggests the patient has been persistently hyperglycemic, while low

concentrations imply prolonged periods of hypoglycemia (**TABLE 2**).

Factors affecting serum protein concentrations and protein turnover can affect fructosamine. In cats, conditions associated with reduced protein intake, protein-losing disorders, and hyperthyroidism have been shown to reduce measured fructosamine concentrations.[27,29] While the fructosamine concentration is often used initially to diagnose persistent hyperglycemia, in the monitoring phase of diabetic management it is simply another tool used to judge relative glycemic control.[28] It is important to remember that the measured result represents an average glucose level over time; therefore, short periods of hypoglycemia can occur without detection if there are prolonged bouts of hyperglycemia.

Urine Glucose Evaluation

Glucose appears in the urine once the threshold for renal tubular reabsorption is exceeded. The average renal tubular threshold for glucose is around 250 to 290 mg/dL in cats.[30] The urine glucose concentration reflects the total amount of glucose excreted into the urine since the previous micturition event. Therefore, periods of hypoglycemia are masked by bouts of hyperglycemia and excess urinary glucose spillage.

Most patients with clinically well-controlled diabetes (serum glucose between 100 and 300 mg/dL over the course of the day) are expected to have glucosuria. Therefore, urine monitoring may be most helpful in identifying persistent hypoglycemia or diabetic remission, as the cat should consistently test negative for urine glucose. Additionally, urine dipstick strips that detect ketones are useful for monitoring hyperglycemic patients at risk for developing ketoacidosis.

Table 2 General Interpretive Criteria for Fructosamine Concentrations (μmol/L)[a]

>450	Poor diabetic control
400-450	Fair diabetic control
300-400	Good diabetic control
<300	Tightly controlled, diabetic remission onset, or prolonged hypoglycemia

[a]The reference range of the individual laboratory should be used when interpreting patient results.

ASSESSMENT OF INSULIN RESPONSE

BG curve monitoring is typically initiated 7 to 14 days after starting insulin or adjusting the insulin dose. This allows a consistent glycemic response to the insulin dose to develop and optimizes the accuracy of assessment. Once the appropriate insulin dose is found and DM controlled, the frequency of glucose monitoring is typically extended to intervals ranging from 1 to 6 months.

In the authors' experience, most diabetic cats tend to fluctuate within a narrowed glycemic range over the course of the day, unlike dogs. However, the general aim of hyperglycemic treatment is to have a BG nadir of ~100 mg/dL, with an overall range during the curve period between 100 and 300 mg/dL. Treatment decisions are ideally made using a BG curve interpretation in conjunction with other factors such as the presence of clinical signs, changes in BW, or a fructosamine concentration.

Standard Blood Glucose Curve

Evaluating the glycemic response to a prescribed insulin dose involves obtaining serial BG readings before and then every 2 to 4 hours after insulin administration using a veterinary-calibrated handheld glucometer. Variables assessed by a BG curve include the pre-insulin BG concentration, onset of insulin action, maximum insulin response (BG nadir), duration of insulin action, and range of BG over the dosing interval. Since all aspects of a patient's insulin response are represented, this is the ideal monitoring tool to direct changes to insulin therapy. However, information should be interpreted in light of the factors discussed above.

Sampling Considerations

A veterinary-specific glucometer should be used, as those calibrated for people often underestimate veterinary patient BG concentrations.[31] A skin prick to obtain a capillary whole blood bleb is most commonly performed; however, the use of serum or plasma samples has been reported to result in less variability.[32] Peripheral body sites sampled in cats include the lateral aspect of the pinna, the pisiform pad, and the metacarpal/tarsal pads (**FIGURES 2 AND 3**).[33-36] The authors typically compare a BG reading from the selected sample site with a jugular venous BG reading to ensure relative accuracy before proceeding with long-term monitoring.

Consideration should be given to the pricking device (needle or spring-loaded lancet) used in cats, as lancets were less likely to be associated with causing a pain response in dogs (unpublished data).[a] Additionally, while warming a cat's ear before pricking may increase the likelihood of getting a sufficiently sized bleb, squeezing pricked sites increased the chance of obtaining an erroneous result compared with a

FIGURE 2. Glucose measurement using ear prick in a cat.

simultaneously obtained jugular venous BG in dogs (unpublished data).

Home Monitoring
In-hospital BG curves have inherent flaws that can affect how results are interpreted. The stress associated with travel to the hospital, lack of acclimatization to a new environment, handling for repeated sampling, and/or disruption of normal daily activities can all affect glycemic regulation and curve results. This has led to most consensus recommendations suggesting the use of home monitoring in cats, where owners generate BG curves for veterinary interpretation.[7,37]

Although home monitoring minimizes the influence of some stressors, it can contribute to client anxiety and a strained human-animal bond if owners unnecessarily oversample their pet's BG.[38] Owners can also develop a false sense of confidence over time and may begin adjusting insulin doses without the direction of a veterinarian. So while at-home curves can be useful when done appropriately, a successful home monitoring program requires careful client-patient selection and exceptional client-veterinarian communication.

With a clearly defined monitoring protocol, clients are typically capable of performing curves and are overall satisfied with the home monitoring process.[38,39] Clear expectations and guidelines should be set for clients to follow and report back the necessary information required to manage their pet. Home monitoring does not mitigate the need for regular in-hospital evaluations, and clients have been shown to maintain continuity of in-hospital care for their cat while performing home monitoring.[39]

Role in Patient Management
Several studies have documented large day-to-day variability in BG curve results obtained in both hospital and home environments.[40,41] This highlights the fact that BG curves are only one tool in comprehensive diabetic patient assessment and should be interpreted concurrently with other clinical data (such as presence of clinical signs) to maximize accuracy of treatment recommendations. For most diabetic cats, the authors recommend intermittent glucose curve assessment and prefers home monitoring when appropriate. However,
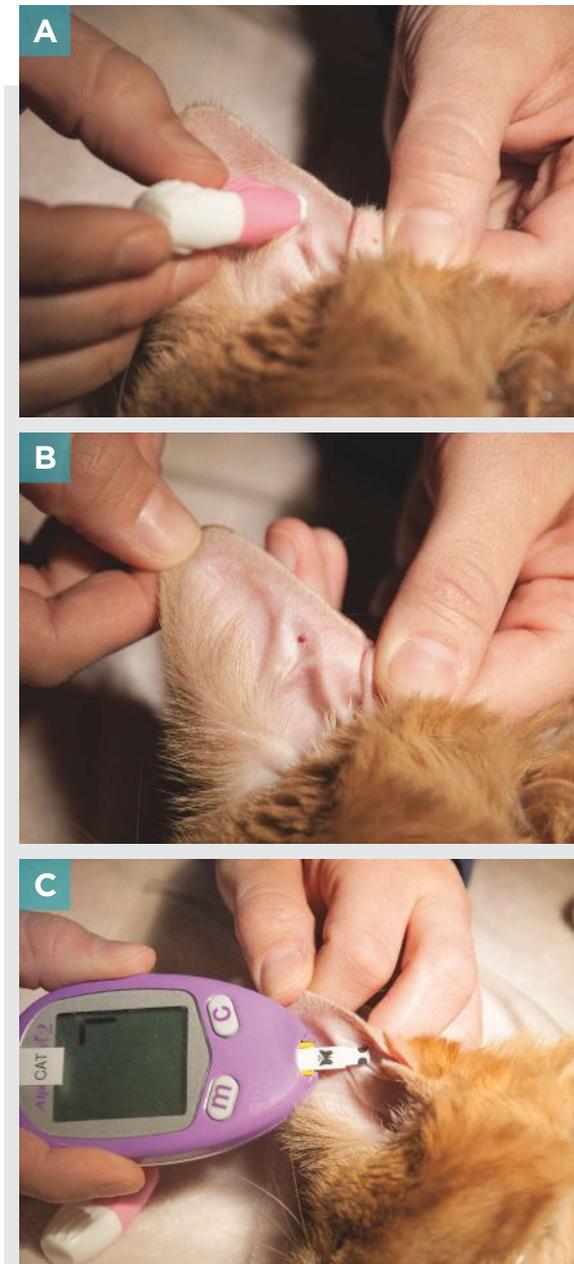
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[a]Bugbee A, Ward C. (2013). Validation of pediatric spring-loaded lancets to obtain capillary glucose readings at various body sites in healthy dogs.

glucose monitoring of any kind may be impractical in some cats (i.e., those that are fractious in-hospital and at home). Therefore, serial glucose monitoring may have to be replaced by a combination of other monitoring tools, such as clinical signs and fructosamine concentrations, to obtain information to guide therapeutic decision-making.

Continuous Interstitial Glucose Monitoring

The continuous interstitial glucose monitoring (CIGM) process involves implantation of a subcutaneous catheter (sensor) that facilitates measurement of the interstitial fluid (ISF) glucose concentration. The device uses glucose oxidase to produce an enzymatic reaction, which is converted into an electrical signal for measurement. The ISF glucose concentration has been shown to correlate with the BG concentration, although there is a 5- to 12-minute delay before acute changes in the BG are reflected in the ISF.[42,43] The device validated for use in cats (iPro2, Medtronics) samples ISF glucose every few seconds, and an external transmitter records readings every 5 minutes (equating to 288 readings per 24 hours). Thus, the greatest advantage of CIGM is in providing a huge amount of glycemic data obtained over 3 to 5 days with the patient in its home environment. The major disadvantages of the validated CIGM system are the requirement to obtain a minimum of 2 glucometer-derived BG readings per day for calibration purposes and a manufacturer-reported working range of only 40 to 400 mg/dL.

A novel flash glucose monitoring system (FreeStyle Libre, Abbot) uses a disposable sensor that can be worn for up to 14 days and measures ISF glucose every minute.[44] The reported working range is between 20 and 500 mg/dL, and the device is factory calibrated, thereby mitigating the need for any glucometer-derived calibrations. An external handheld reader containing a built-in glucometer system (FreeStyle Precision, Abbot) can be held up to the implanted sensor to digitally display a real-time glucose reading as well as trend historical results within a 15-minute period.[45] The accuracy and performance of this device have been validated for use in dogs, but there are only anecdotal reports of successful use in cats.[44] **TVP**

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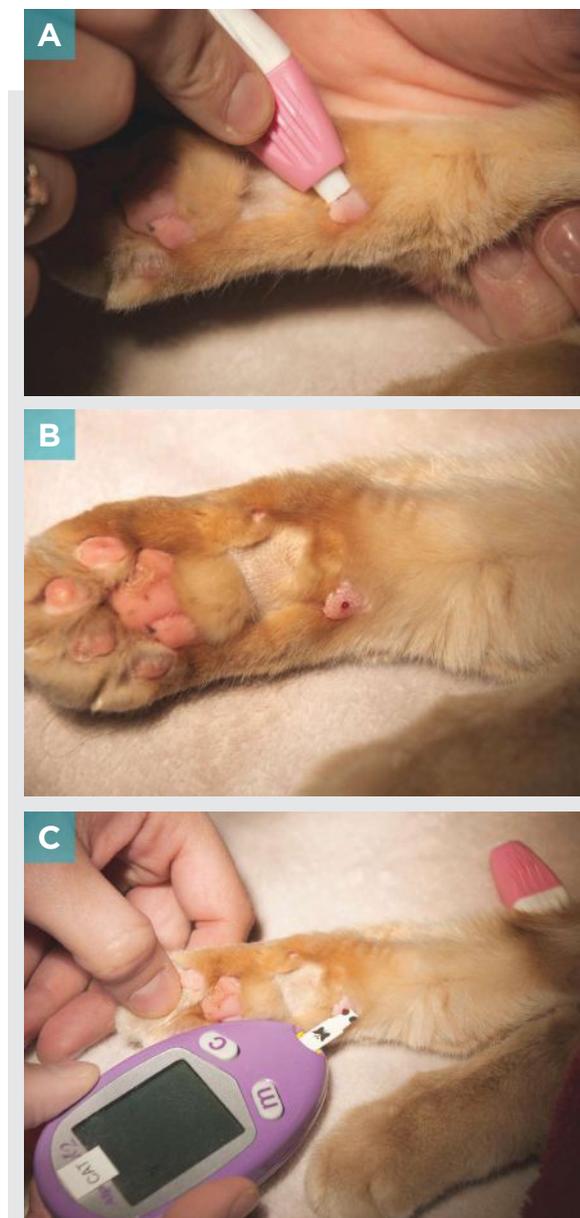
FIGURE 3. Glucose measurement using paw prick in a cat.

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