Updates in Feline Diabetes Mellitus and Hypersomatotropism

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KEYWORDS

• Ketoacidosis • Remission • Acromegaly • Glycemic variability

KEY POINTS

- Flash glucose monitoring is a useful addition to standard blood glucose monitoring and can provide frequent, noninvasive glucose measurements in a variety of settings.
- Hypophysectomy is the gold standard treatment of hypersomatotropism-associated diabetes in cats and offers a good chance of cure of hypersomatotropism and diabetes mellitus.
- Toujeo insulin glargine seems to provide a more flat, constant activity profile than other long-acting insulins and could be particularly effective in cats with glycemic variability.

This article uses a case-based approach to explore the current evidence on feline diabetes mellitus (DM) treatment and how to best apply this evidence in clinical situations. These cases also discuss novel concepts in feline DM management, including flash glucose monitoring, novel insulin preparations, and hypophysectomy for the treatment of hypersomatotropism (HS).

CASE 1: SICK DIABETIC CAT, MONKEY, A 12-YEAR-OLD NEUTERED MALE DOMESTIC SHORTHAIR

Presentation

- Inappetence for 3 days
- Vomited once yesterday
- Increased thirst for 1 week
- Depressed mentation for 1 day
- Plantigrade gait for 1 day

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- No other recent health concerns

Initial Examination

- Weight: 7.8 kg
- Body condition score (BCS): 7.5/9
- Muscle score: 2/3 (mild muscle loss)
- Mentation: quiet, responsive
- Hydration: slightly tacky oral mucosa
- Vital signs: heart rate 170/min, respiratory rate 24/min, temperature 38.3°C (**Box 1**)

Assessment

Does this cat have diabetes mellitus or stress hyperglycemia?

Presence of ketosis is useful to distinguish diabetic from nondiabetic sick cats and is more reliable than fructosamine.[1] Although there is no information yet about blood ketones in this case, the presence of ketonuria indicates that ketosis and therefore DM is likely. Semiquantitative blood/serum ketone measurement is easily performed by applying a drop of serum or plasma to the ketone test patch of a urine dipstick, which provides a colorimetric indication of acetoacetate ± acetone concentration.[2] Point-of-care handheld ketone meters, which measure β-hydroxybutyrate, are also reliable in cats. These are likely to be more sensitive for the detection of ketosis due to β-hydroxybutyrate being the predominant ketone body in ketosis secondary to DM. They also provide a rapid, quantitative measurement, which can be used to monitor patient progress.[3,4]

Is there ketoacidosis (diabetic ketoacidosis) and/or hyperosmolality?

Although ketosis is likely, identification of decreased blood pH and/or decreased plasma bicarbonate concentration is required to diagnose acidosis. However, when this is unavailable, the European Society of Veterinary Endocrinology ALIVE guidelines recommends that diabetic patients who are unwell "should be suspected of suffering

Box 1
Initial in-house clinical pathology results for monkey

Blood glucose (BG): 513 mg/dL (reference interval [RI] 70 to 150 mg/dL) (28.5 mmol/L [RI 3.9–8.3 mmol/L])

Plasma albumin: 4.5 g/dL (RI 2.2–4.4 g/dL) (45 g/L [RI 22–44 g/L])

Plasma urea: 38.8 mg/dL (RI 10.0–30.0 mg/dL) (13.6 mmol/L [RI 3.6–10.7 mmol/L])

Plasma creatinine: 2.32 mg/dL (RI 0.30–2.00 mg/dL) (211 μmol/L [RI 27–186 μmol/L])

Plasma alanine aminotransferase: 107 U/L (RI 20–100 U/L)

Plasma alkaline phosphatase: 48 U/L (RI 10–90 U/L)

Plasma sodium: 147 mEq/L (RI 142–164 mEq/L) (147 mmol/L [RI 142–164 mmol/L])

Plasma potassium: 3.9 mEq/L (RI 3.7–5.8 mEq/L) (3.9 mmol/L [RI 3.7–5.8 mmol/L])

Plasma chloride: 110 mEq/L (RI 110–126 mEq/L) (110 mmol/L [RI 110–126 mmol/L])

Urine specific gravity: 1.023

Urine glucose: 4+

Urine ketones: 2+

from diabetic ketoacidosis (DKA)."[5] Diabetic cats that are inappetent or anorexic should be assumed to be unwell because DM generally causes polyphagia, unless complicated by another condition.

Estimated osmolality is 344 mOsm/kg (**Box 2**). Patients are considered hyperosmolar at an osmolality greater than 320 mOsm/kg, whereas the more complicated hyperosmolar hyperglycemic state is usually associated with osmolality greater than 340 mOsm/kg and BG greater than 600 mg/dL (>33 mmol/L).[6]

Therefore, Monkey should commence treatment of DKA and possible hyperosmolar hyperglycemic state. Treatment of these two conditions is similar and, although it will be useful to have additional diagnostic information in due course, there is already sufficient information to begin treatment without delay. Importantly, DKA in cats with newly diagnosed DM does not affect survival time,[7] and these cases can often go on to achieve diabetic remission.[8] One important negative prognostic indicator in cats with newly diagnosed DM is higher plasma creatinine concentration.[7] It is therefore noteworthy that Monkey's creatinine is only mildly increased, despite dehydration and hyperosmolality. Although it is difficult to assess renal function in diabetic cats with dehydration and osmotic diuresis, chronic kidney disease is not more frequent than in nondiabetic cats.[9]

Goals of Treatment in Sick Diabetic Cats

- Gradually replace body fluid deficit
- Slowly decrease plasma osmolality and BG concentration
- Halt and prevent ketogenesis
- Restore electrolyte and acid-base balance
- Identify and manage any underlying or precipitating factors

Fluid and Electrolyte Therapy

- No published studies have compared the efficacy of different fluid types in sick diabetic cats, but 0.9% saline or lactated Ringer solutions are commonly recommended.[6,10,11]
- A conservative fluid rate is recommended to avoid overhydration and major osmotic shifts. Flow rates 1.5 to 2 times normal maintenance requirements (4–6 mL/kg/h) are therefore appropriate. This aligns with the current perspective for human pediatric patients with DKA that advocates a "one size fits all" strategy with slow and even correction of fluid deficit.[12]
- It is important to calculate rates based on estimated ideal body weight in underweight or overweight cats. Because Monkey has an overweight body condition, it

Box 2
Estimation of plasma osmolality

Estimated osmolality (mOsm/kg) = $2*(Na^+ + K^+)$ + glucose (mg/dL)/18 + blood urea nitrogen (mg/dL)/2.8

[or $2*(Na^+ + K^+)$ + glucose (mmol/L) + blood urea nitrogen (mmol/L)]

The main determinant of osmolality is sodium; glucose has less impact unless there is severe hyperglycemia. Therefore, effective osmolality can alternatively be calculated using the simplified formula:

Effective osmolality = $2*Na^+$ + glucose (mg/dL)/18 [or $2*Na^+$ + glucose (mmol/L)]

is prudent to use an estimation of ideal body weight (eg, 5.5 kg) for all dose calculations.

- Maintenance fluids should be supplemented with 30 to 40 mEq/L (30–40 mmol/L) of potassium (KCl or a 50:50 combination of KCl and KPO_4) from the outset. Sick diabetic cats have a high risk of hypokalemia even if plasma potassium concentration is not decreased at presentation. Potassium depletion results from reduced intake caused by anorexia, and increased loss caused by vomiting and diuresis. Fluid therapy causes dilution of circulating potassium concentrations and promotes further renal loss, whereas insulin therapy and correction of acidosis results in movement of potassium out of the extracellular space into cells. In critically ill patients, adjustment of fluid potassium supplementation should ideally be based on results of plasma potassium concentration monitoring.[6,11] Such intensive monitoring is usually not required for cats that rapidly recover a normal or polyphagic appetite while treated with fluids supplemented with potassium as recommended previously.

Insulin Therapy

- Insulin treatment should commence when practical. Cats with DKA recover more rapidly if insulin treatment commences within 6 hours after admission[13] and higher concentrations of intravenous (IV) insulin result in better clinical outcomes.[14] Although fluid therapy corrects many metabolic derangements and causes BG to decrease, it does not switch off ketogenesis, which is the catalyst for DKA. In fact, before insulin was commercially available, DKA was almost uniformly fatal.
- Rapid-acting insulin, such as regular (soluble) insulin, is administered as an IV constant rate infusion (CRI) or as repeated intramuscular (IM) and subcutaneous (SC) injections.[6,10,11] Other rapid-acting options are insulin lispro[15] and aspart.[16] If rapid-acting insulin is unavailable, Lantus glargine is substituted in CRI protocols because it has a similar action to regular insulin when delivered by IV.[17]
- CRI protocols are often simpler and less labor intensive for prolonged management of sick diabetic cats. The main constraint is that a separate fluid infusion pump is required in addition to that used for supportive fluid therapy. **Box 3** and **Fig. 1** provide a simple, "one size fits all" insulin CRI protocol that is appropriate for Monkey.
- Protocols of repeated IM and SC injections are also effective. The most common protocol comprises an initial 0.2 U/kg dose of regular insulin administered IM and followed with SC doses at 0.1 U/kg every hour. Ongoing insulin doses are then adjusted based on BG monitoring at least once hourly.[18]
- Glargine can also be used IM and SC for the management of sick diabetic cats.[19,20] A protocol using intermittent IM/SC injections of glargine and regular insulin was established as an alternative to insulin CRI for treatment of DKA in cats.[20] Glargine was administered at a dose of 0.25 U/kg every 12 hours. BG was checked every 2 to 4 hours and the following actions taken:
  - 1 U regular insulin was administered every 6 hours when BG was greater than 250 mg/dL (>14 mmol/L)
  - 2.5% glucose CRI was given when BG was 80 to 250 mg/dL (4.4–13.8 mmol/L)
  - An IV bolus of glucose plus ongoing CRI with 5% glucose was given if BG was less than 80 mg/dL (<4.4 mmol/L).[20]

Box 3
"One size fits all" insulin CRI protocol for sick diabetic cats

- Add 25 U (0.25 mL) regular insulin to 500 mL saline or lactated Ringer solution (or 50 U [0.5 mL] to 1000 mL solution), resulting in a 50 mU/mL solution. Cover the fluid bag to protect insulin from light.
- Priming the line is unnecessary. Some insulin adsorbs to the lining of the infusion bag and giving set, but this soon reaches steady state and all remaining insulin is delivered to the animal. It is also not necessary to run the insulin CRI through a separate IV catheter. In fact, it is prudent to run concurrent insulin and glucose infusions through the same catheter to ensure that both infusions cease at the same time if the catheter fails.
- An initial insulin infusion rate of 50 mU/kg/h is recommended, achieved by administering the previously mentioned solution at 1 mL/kg/h (calculated using estimated ideal body weight).
- This rate is halved to 25 mU/kg/h (0.5 mL/kg/h of this solution) when BG reaches 180 to 270 mg/dL (10–15 mmol/L). At the same time, maintenance fluids should be changed to contain 2.5% dextrose in 0.45% saline supplemented with 30 to 40 mEq/L (30–40 mmol/L) potassium.
- A reliable means of achieving a fairly stable BG concentration in an anorexic diabetic cat is to balance IV infusion of insulin at 25 mU/kg/h (0.5 mL/kg/h) with 2.5% dextrose in 0.45% saline supplemented with potassium at 6 mL/kg/h. This is the safest option whenever close monitoring is not possible.
- Insulin infusion rate is adjusted up or down to maintain BG at 145 to 270 mg/dL (8–15 mmol/L). If the cat's illness is associated with substantial insulin resistance (IR), an insulin infusion rate of up to 150 mU/kg/h (3 mL/kg/h of the solution described previously) may be required to maintain BG at 145 to 270 mg/dL (8–15 mmol/L).
- When a previously anorexic diabetic cat begins to eat, the IV insulin rate might need to be increased to manage increased glycemia.
- See **Fig. 1** for an example flow chart for hospital use.

Glucose Monitoring

- The standard method for monitoring glucose response to treatment is serial measurement of BG concentration. Blood samples can be obtained by direct venipuncture, although use of a central venous catheter or the marginal ear vein are typically more comfortable and less stressful for the cat.[10]
- Veterinary glucose meters that have been validated using feline samples are recommended for monitoring sick diabetic cats, although meters intended for human use can also be reliable.[21–23]
- Continuous glucose monitors (CGMs) measure interstitial glucose and can supplement traditional BG measurement in hospitalized cats.[24] CGMs may be less accurate in cats when there is hypoglycemia,[25] but importantly can detect low glucose values that would have been missed by intermittent BG testing.[26] The working range of these systems is not a practical limitation in the clinical setting. For treatment decisions, it is usually sufficient to know that an animal's glucose concentration is less than 40 mg/dL (<2.2 mmol/L) or greater than 400 mg/dL (>22.2 mmol/L). In this situation, BG measurement is performed if a more accurate result is required.
- The Abbott FreeStyle Libre glucose monitoring system (Abbott Park, Illinois) is an innovative and inexpensive means of monitoring interstitial glucose that is simple to use.[27] The FreeStyle Libre system consists of an adhesive sensor, which samples interstitial glucose concentration every minute and stores these readings for

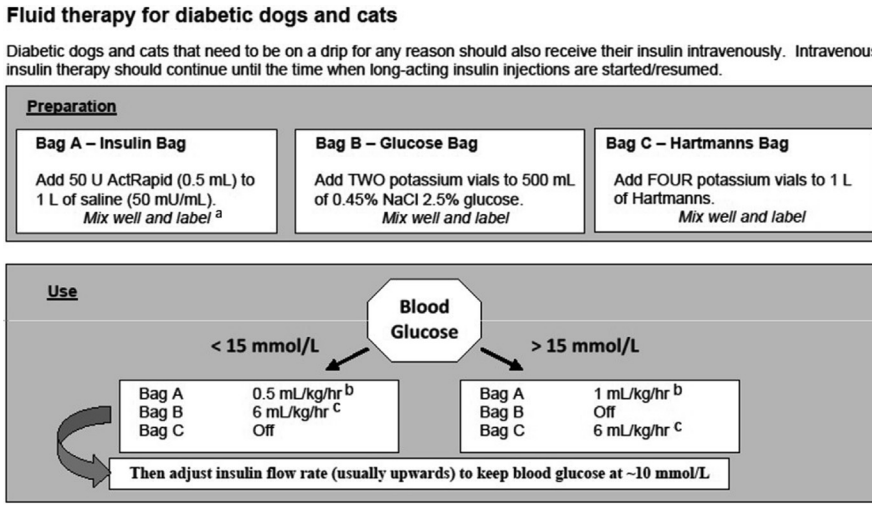

Fig. 1. Example of a fluid therapy flow chart for use in hospitalized diabetic cats. [a] Cover bag to avoid exposure to light. [b] Flow rates are a guide only. Adjust to achieve desired blood glucose concentration. [c] This is approximately twice maintenance. Animals with increased fluid requirements can have the remaining additional fluid rates provided by Bag C. All doses should be based on estimated ideal body weight and not actual body weight.

up to 8 hours (Fig. 2). Whenever the sensor is scanned with the provided scanner, or smartphone App, a flash of the current and previous 8 hours of interstitial glucose data are obtained and a trend arrow is displayed to show whether glucose is increasing, decreasing, or changing slowly. The system requires no calibration and each sensor lasts up to 14 days, although sensor life is typically shorter in cats.

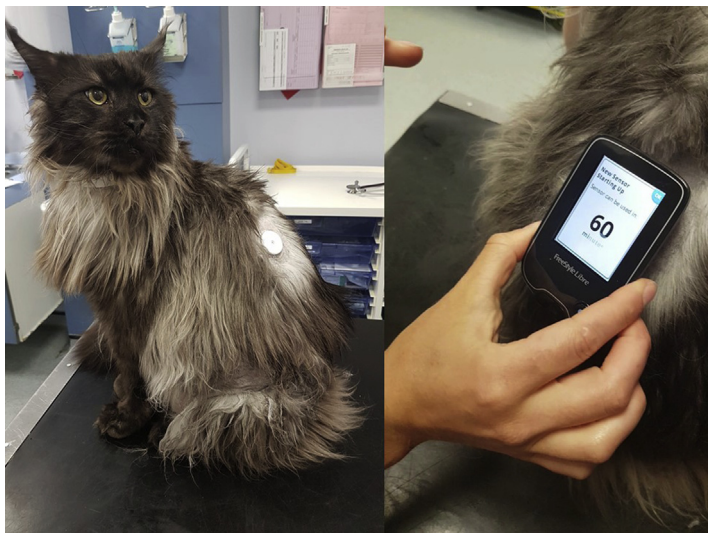

Fig. 2. A Maine Coon with an adhesive glucose sensor for a flash CGM placed on its epaxial area (*left*). The sensor can be scanned to download glucose data (*right*).

- Treatment decisions should not be based solely on interstitial glucose monitoring results. Instead, the FreeStyle Libre can identify changing glucose trends that are confirmed by standard BG testing and thereby facilitate timely treatment decisions. If used correctly, flash glucose monitoring can thus improve patient comfort by decreasing needle sticks while also reducing staff workload. **Box 4** provides tips for use of FreeStyle Libre flash glucose monitoring in sick diabetic cats.

Outcome

- Monkey improved rapidly with fluid and insulin therapy, along with SC maropitant to manage nausea. When hematology, biochemistry, and urinalysis results were returned from the external reference laboratory, they did not identify any significant concurrent problems. He regained a polyphagic appetite within 12 hours and was discharged home after 24 hours with long-acting insulin therapy every 12 hours for maintenance. The FreeStyle Libre sensor remained in place to provide glucose monitoring and helpful feedback to his owners as they became accustomed to the home treatment regimen.
- Monkey continued to have a weak hind leg gait at home, which progressed to generalized weakness unassociated with hypoglycemia. Oral potassium gluconate supplementation resulted in rapid resolution of severe weakness, although a mild plantigrade gait persisted. Potassium depletion myopathy is an important differential diagnosis in cats for diabetic neuropathy and hypoglycemia. Factors that promote potassium depletion in diabetic cats include polyuria and insulin treatment.[28] Improvement in response to oral potassium gluconate supplementation typically occurs within 1 to 2 days with full recovery within 2 to 3 weeks.[29]
- Monkey achieved diabetic remission that lasted for many years after 7 weeks of insulin treatment.
- The residual plantigrade gait presumably caused by diabetic neuropathy gradually resolved by 3 months.

Box 4
Tips for use of FreeStyle Libre glucose monitoring in hospitalized diabetic cats

- A FreeStyle Libre glucose sensor should be applied when practical after hospital admission. This allows glucose monitoring during hospitalization and also for several days after discharge.
- Interstitial and BG results must be clearly differentiated on hospital charts. Two separate columns/rows are therefore required.
- The system does not provide alarms for high or low glucose so must be actively monitored. For example, a veterinarian may write an order to "decrease the insulin CRI rate to 2 mL/h when the BG is <270 mg/dL (<15 mmol/L)." A technician can then periodically scan the sensor every 1 to 2 hours without disturbing the cat and record the times and glucose results on the patient's chart. Once interstitial glucose concentration decreases to less than 270 mg/dL (<15 mmol/L), this is confirmed by testing BG and the insulin treatment adjusted.
- It is helpful to pay attention to the trend arrows and review the graph displayed on the device's reader.
- Any unexpected interstitial glucose results should be checked against BG concentration.
- Once every 24 hours, it is helpful to use the FreeStyle Libre software or LibreView to generate a detailed PDF report and attach this to the patient's file so it is readily accessed by the veterinarian when reviewing overall progress.

- He steadily lost weight and achieved an ideal body weight of 5.5 kg after 5 months.

CASE 2: CAT WITH HYPERSOMATOTROPISM-ASSOCIATED DIABETES MELLITUS, BONNIE, AN 11-YEAR-OLD FEMALE NEUTERED DOMESTIC LONGHAIR

Presentation

- DM diagnosed 4 months previously and treated with Lantus insulin glargine every 12 hours since diagnosis.
- Persistently poor glycemic control, despite increasing insulin dosage.
- Obvious polyuria and polydipsia (PUPD), and extreme polyphagia. Overweight with minimal weight loss (200 g) since diagnosis.
- Currently receiving 10 U (1.8 U/kg) glargine every 12 hours and fed a carbohydrate-restricted, wet commercial diet.
- Recent serum fructosamine 680 μmol/L (RI 249–320 μmol/L).
- Home BG measurements persistently greater than 360 mg/dL (>20 mmol/L) throughout the day.
- Presented for assessment of IR.

Examination

- See **Fig. 3** for patient photograph and oral examination
- Weight: 5.5 kg
- BCS: 6/9
- Muscle condition score: 2/3 (mild muscle loss)
- Alert, appropriate mentation
- Moderate hepatomegaly, mild prognathism inferior (see **Fig. 3**B); examination otherwise unremarkable

Assessment

It is vital to first exclude problems of insulin administration and/or storage when assessing cats with apparent IR. These were excluded in Bonnie's case. Many concurrent conditions can contribute to IR in feline diabetics (**Box 5**), but several features make HS a likely cause in Bonnie's case. HS can cause particularly profound IR compared with other comorbidities, which is consistent with Bonnie's persistent, marked hyperglycemia, despite substantial insulin dosing. Extreme polyphagia, as

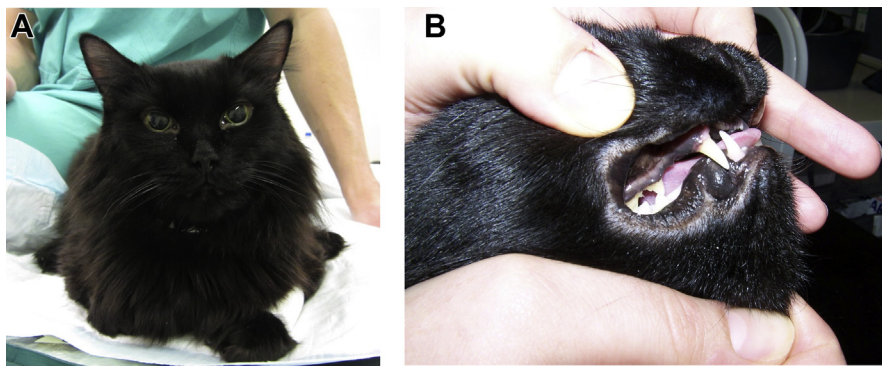

Fig. 3. Patient photographs demonstrating subjectively broad facial features (*A*) and prognathism inferior (*B*).

Box 5
Causes of insulin resistance in cats with DM (not exhaustive)

- Obesity
- Hypersomatotropism
- Hyperadrenocorticism
- Hyperthyroidism
- Exogenous glucocorticoids or progestogens
- Pancreatitis
- Chronic kidney disease
- Gastrointestinal disease
- Any chronic inflammatory disease

seen in Bonnie, is a common finding in cats with HS.[30] Bonnie's subjective facial broadening and prognathism inferior (see Fig. 3) suggest she is affected by acromegaly, which results from the mitogenic effects of excess growth hormone. However, only a proportion of cats with HS-associated DM have noticeable acromegaly and its absence should not exclude the possibility of HS.[30,31] Index of suspicion for HS would be particularly great if practicing in a country with a high reported prevalence of HS among diabetic cats. HS has been estimated to cause approximately 25% of feline DM cases in the United Kingdom.[30] However, this could be an overestimation because of veterinarians' being more likely to submit samples for the study's free insulin-like growth factor-1 (IGF-1) measurement from cats with possible signs of HS. An alternative study from Switzerland and the Netherlands reported an estimated prevalence of 17.8% among diabetic cats.[32]

Serum IGF-1 measurement was submitted and was supportive of HS (239 nmol/L [1825 ng/mL]; RI <130 nmol/L [<1000 ng/mL]).

Are further diagnostic tests necessary to confirm hypersomatotropism?

A serum IGF-1 concentration of greater than 130 nmol/L (>1000 ng/mL) has a positive predictive value of 95%[30] for HS so, in combination with Bonnie's consistent clinical findings, is highly suggestive of HS. Pituitary imaging with computed tomography or, less often, MRI is often used to support the diagnosis by demonstrating pituitary enlargement. Despite this, 3% to 4% of cases have a normal pituitary size on diagnostic imaging[30] and this percentage is likely to increase with improved awareness and earlier detection of cats with HS. HS should therefore not be excluded based on a normal pituitary appearance on advanced imaging. Pituitary imaging also provides information that is relevant to several treatment modalities (Table 1).

What are the major treatment options for hypersomatotropism-associated diabetes mellitus?

Table 1 shows the main treatment options for HS-associated DM in cats.

Treatment Plan

Bonnie underwent hypophysectomy to provide the greatest chance of cure of HS and resolution of DM. Preoperative cranial computed tomography revealed moderate pituitary enlargement (ventrodorsal height 8 mm, normal $\leq$4 mm[33]) (Fig. 4). The extent of

Table 1
Main treatment options for cats with HS-associated DM

Treatment	Rationale	Advantages and Disadvantages
Standard DM management only	Attempts to manage the diabetogenic effects of GH excess only	Advantages Widely accessible option Might maintain an acceptable quality of life for a period of time Disadvantages Does not treat the pituitary tumor or mitogenic effects of GH (eg, acromegalic changes) DM control often poor with severe ongoing DM signs Large insulin doses potentially required, which is costly Large insulin dosage makes hypoglycemic episodes possible when pulsatile GH secretion is low
Radiotherapy	Targeted radiation energy preferentially damages pituitary tumor tissue Several protocols described including, recently, stereotactic[46–48]	Advantages Improved DM control common, with 30%–40% diabetic remission rate Might shrink tumor, and thus improve any neurologic signs Disadvantages Typically, weeks to months for improvement to become apparent IGF-1 and mitogenic effects of GH do not normalize Relapse common Limited availability Costly Repeated anesthesia required (fewer with stereotactic)
Transsphenoidal Hypophysectomy	Surgical pituitary removal	Advantages[49] Removes tumor Normalization of IGF-1 and cure of HS in >90% of cats Approximately 70% DM remission rate Disadvantages Limited availability Costly Associated mortality (<10%) Long-term hormonal replacement required
Cryohypophysectomy	Surgical cryoablation of the pituitary gland	Advantages Destroys tumor tissue Decreased IGF-1 in the only 2 cases reported[50,51] Disadvantages Little clinical experience, limited availability Costly

(*continued on next page*)

Table 1
(*continued*)

Treatment	Rationale	Advantages and Disadvantages
Pasireotide	Injectable somatostatin analogue; inhibits GH secretion from pituitary tumor	Advantages Improved DM control common, with diabetic remission rates of approximately 20%–25%[52] Generally well-tolerated Disadvantages IGF-1 and mitogenic effects of GH do not normalize Does not treat tumor Limited availability Costly Self-limiting diarrhea common
Cabergoline	Dopamine agonism causing inhibition of pituitary GH release	Advantages Widely available Low-cost Generally well-tolerated Disadvantages Little clinical experience, might improve glycemic control in individual cats at dose of 5–10 μg/kg PO SID,[53] further research warranted

Abbreviation: GH, growth hormone.

acromegalic cardiomyopathy was assessed preoperatively using echocardiography to guide anesthesia and perioperative fluid therapy.

Preoperatively, an Abbott FreeStyle Libre flash glucose monitoring system was applied to provide frequent, noninvasive interstitial glucose measurement during the perioperative period (Fig. 5). Hypophysectomy was performed via a transsphenoidal approach through the oral cavity (Fig. 6).[34]

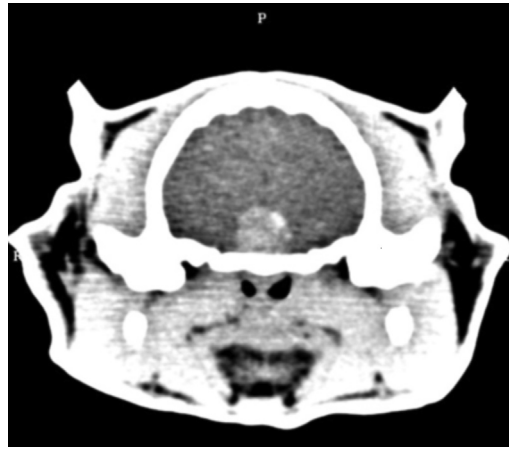

Fig. 4. Transverse cranial computed tomography image showing pituitary enlargement.

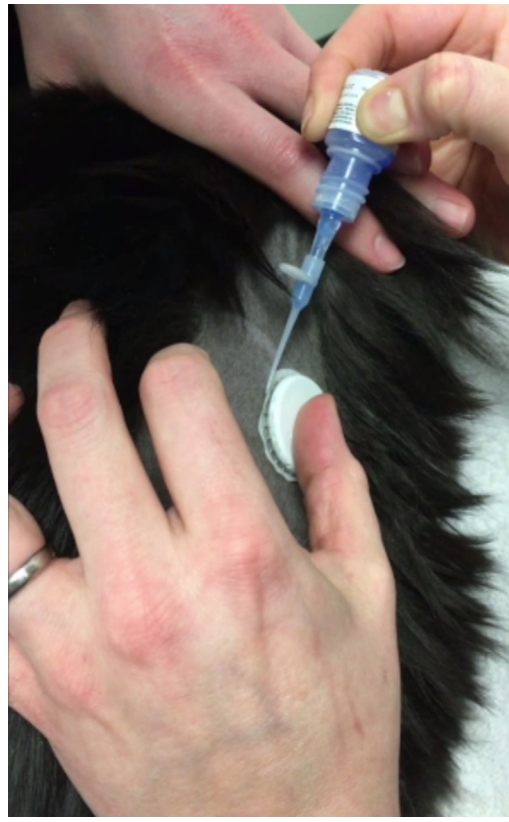

Fig. 5. A flash glucose sensor is applied to Bonnie's lateral thoracic wall. Small drops of tissue glue are applied to the adhesive layer for additional security.

What Are the Medical Considerations Following Hypophysectomy?

- To control hyperglycemia, cats receive a CRI of 0.9% NaCl with soluble insulin ± dextrose from anesthesia induction until willing to eat postoperatively, when long-acting maintenance insulin can be reintroduced. At the author's (RG) hospital, a maximum hourly rate of 4 mL/kg/h for all infusions is used to limit risk of volume overload. Cats often eat within 24 hours postsurgery. Insulin sensitivity can rapidly improve following successful surgery (**Fig. 7**) so glucose concentration must be frequently monitored and insulin dose adjusted. Maintenance insulin is typically restarted at a reduced dose compared with preoperatively because of improved insulin sensitivity.
- Treated cats require lifelong glucocorticoid and thyroxine supplementation because of absolute lack of adrenocorticotrophic hormone and thyroid-stimulating hormone, respectively, following hypophysectomy. A hydrocortisone sodium succinate CRI is started immediately before pituitary removal and is continued postoperatively until oral glucocorticoid therapy is introduced. Oral levothyroxine is started once cats can tolerate oral medication.
- Antidiuretic hormone supplementation is required at time of surgery and postoperatively to treat central diabetes insipidus because hypophysectomy causes cessation of antidiuretic hormone secretion by the neurohypophysis.

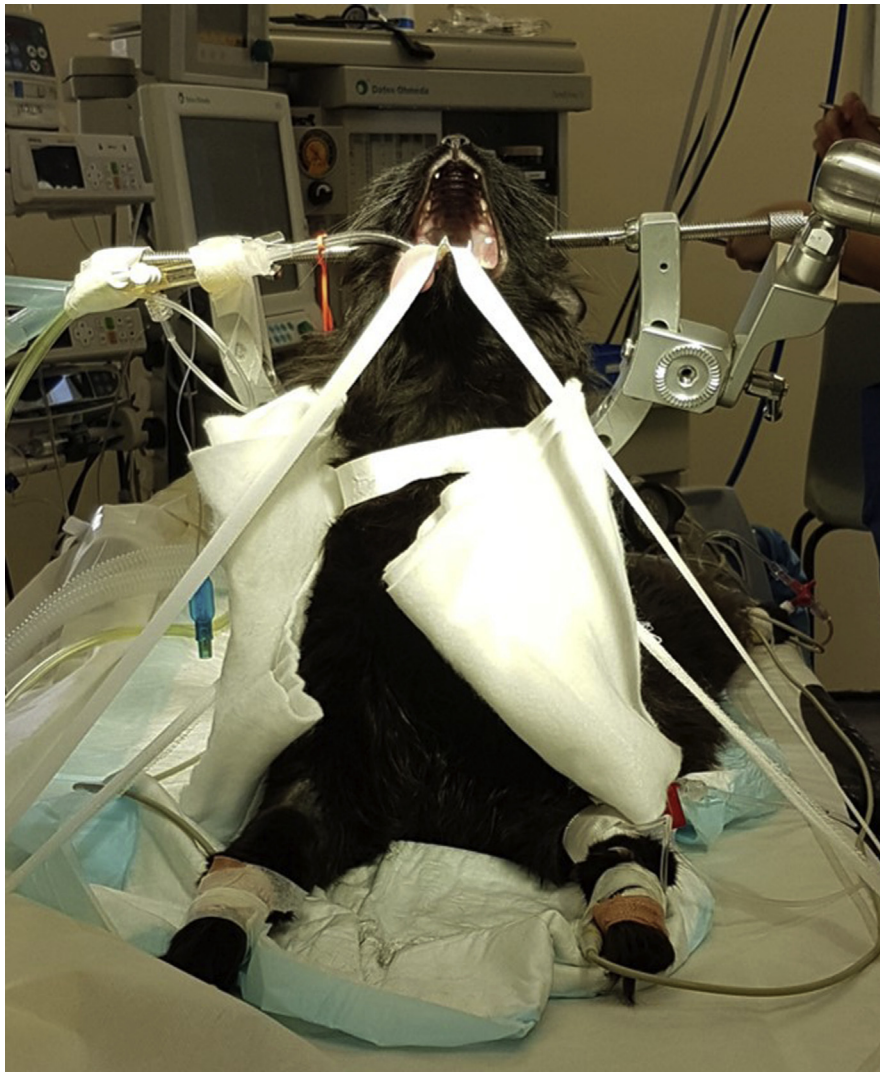

Fig. 6. Patient is positioned (before draping) for transsphenoidal hypophysectomy.

Supplementation can eventually be discontinued in some cats because antidiuretic hormone from the hypothalamus can still be secreted into the systemic circulation via the portal capillaries of the median eminence.[35]

- Prophylactic amoxicillin-clavulanate therapy is given for 2 weeks postoperatively.

Outcome

Bonnie's hypophysectomy proceeded without complication and she was alert and willing to eat within 18 hours of surgery. Conjunctival desmopressin (1 drop every 8 hours) was started during surgery. Hydrocortisone CRI was replaced with oral hydrocortisone (0.5 mg/kg every 12 hours) the day following surgery. Oral levothyroxine (0.1 mg total dose every 24 hours) and a reduced dose of Lantus glargine (3 U every

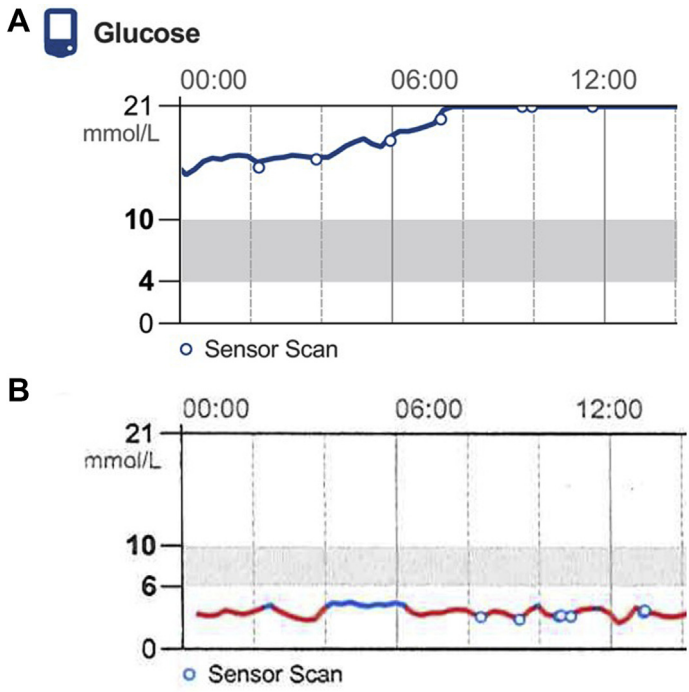

Fig. 7. Interstitial glucose curves, generated using a flash CGM system, before (*A*) and 5 days' after (*B*) hypophysectomy, showing greatly improved insulin sensitivity. (*Courtesy of* J. Cockerill, BVMS, Eaton, Australia.)

12 hours) was introduced 2 days after surgery. Insulin sensitivity noticeably improved during postoperative hospitalization (see Fig. 7) and Bonnie was discharged 1 week postsurgery on a Lantus glargine dose of 1 U SC every 12 hours. Hydrocortisone dose was reduced to 0.5 mg/kg every 24 hours at the time of discharge. One month postoperatively, IGF-1 measurement revealed resolution of HS (8.4 nmol/L [64 ng/mL]), and a serum total thyroxine measurement 5 hours postpill was 55 nmol/L (RI 19–65 nmol/L [4.3 μg/dL (RI 1.5–5.0 μg/dL)]), supporting adequate levothyroxine supplementation. Bonnie was able to discontinue insulin therapy 3 weeks after surgery and went on to achieve sustained diabetic remission. Conjunctival desmopressin frequency was reduced over 3 months following surgery, but discontinuing treatment resulted in PUPD. Therapy was therefore reinstated and continued at 1 drop every 24 hours indefinitely.

CASE 3: EXCESSIVE GLYCEMIC VARIABILITY IN A DIABETIC CAT, MU, A 16-YEAR-OLD NEUTERED FEMALE BURMESE

Presentation

- DM was first diagnosed 6 years ago; remission readily achieved within a few months.
- DM relapsed 2 years ago and Mu subsequently remained insulin-dependent.
- Stable glycemic control has been difficult to achieve over the last year, despite careful adjustment of insulin dose, and Mu has experienced several unexpected episodes of hypoglycemia with mild to severe clinical signs.

Fig. 8. A loose "scarf" (*middle* and *right*) can protect a flash CMS sensor applied to the side of the neck (*left*) and so extend the life of sensors worn in the home environment. This is simply fashioned by pinning together the top and toe of a sock around the neck.

- Insulin treatment was changed 9 months ago from veterinary porcine lente insulin (Vetsulin/Caninsulin) administered every 12 hours with U-40 syringes to Lantus glargine insulin administered every 12 hours with a SoloStar insulin dosing pen. Current dose is 1 U every 12 hours.

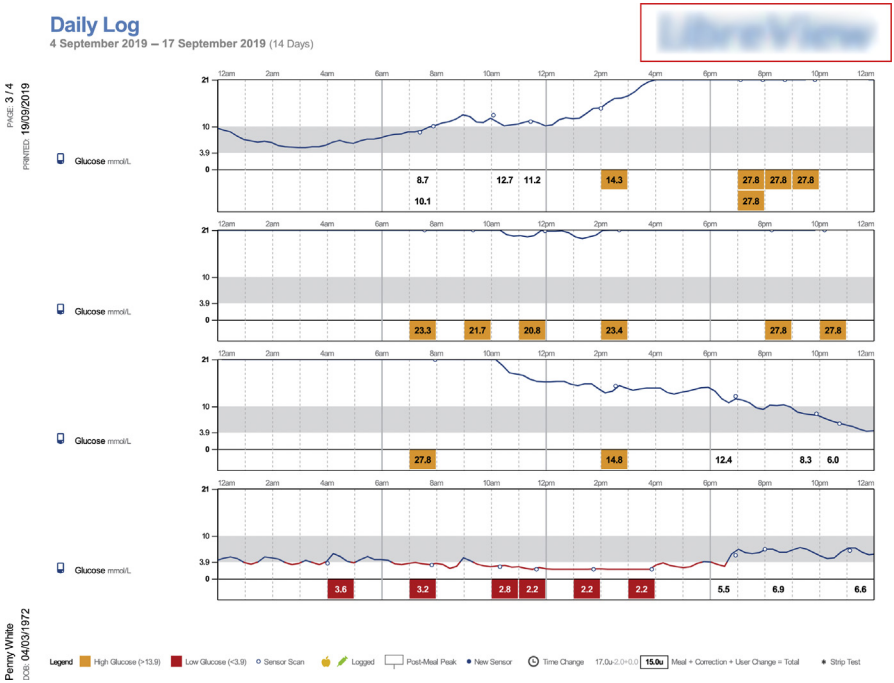

Fig. 9. Interstitial glucose curves from Case 3, generated using a flash CGM system and demonstrating excessive glycemic variability ranging less than 40 to greater than 400 mg/dL (<2.2 to >27.8 mmol/L).

- BG monitoring at home is limited because the owner works long hours. In addition to occasional hypoglycemia, results over several months also frequently identified moderate and severe hyperglycemia (range, 30–685 mg/dL [1.7–38 mmol/L]).
- Mu has a stable body weight, but is often PUPD, and has polyphagia. Urine dipstick testing at home is usually positive for glucose, but a negative result is obtained about once weekly.

Examination

- Weight: 4.7 kg
- BCS: 6/9
- Muscle score: 3/3
- Mentation: alert, appropriately responsive
- Unremarkable physical examination with a soft glossy coat

Assessment

- Several features of Mu's case are consistent with excessive "glycemic variability,"[36] a condition that anecdotally seems to be more common in cats with long duration of DM.
- "Somogyi effect" is also often used to explain periods when hypoglycemia and hyperglycemia occur. A more appropriate term that has been adopted in human

Fig. 10. Side-by-side comparison of the 300 U/mL glargine (*left* in each picture) and 100 U/mL glargine (*right* in each picture) insulin dosing pens. Note all staff and clients must be educated to never draw the 300 U/mL insulin from the dosing pen using a syringe. (*Courtesy of* Sanofi US, Bridgewater, NJ.)

medicine is "glycemic variability."[36–38] The term "brittle DM" has also been used, although this is now less preferred.

- A key observation is failure of increased insulin doses to resolve hyperglycemia. Instead, the cat continues to have poor diabetic control with higher insulin doses but might become prone to unexpected hypoglycemia. Decreasing insulin dose

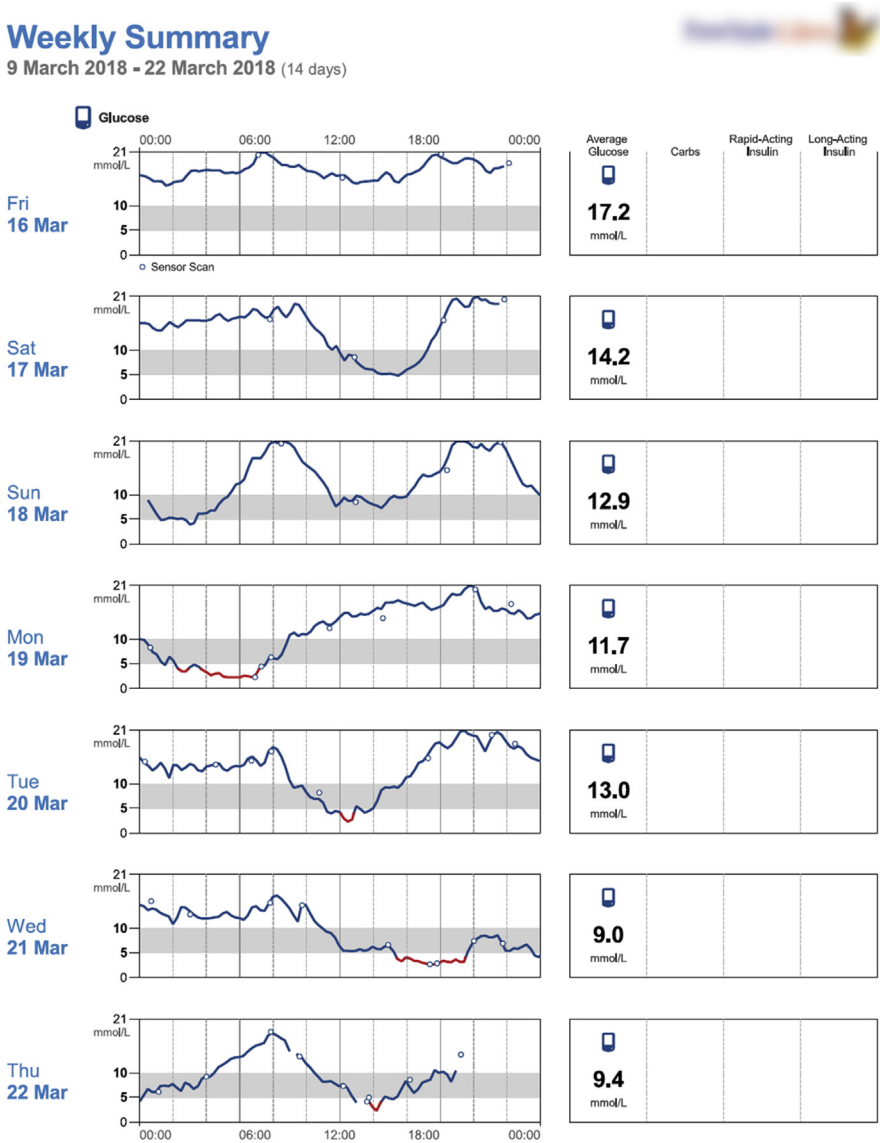

Fig. 11. Interstitial glucose curves generated using a CGM system from a cat with excessive glycemic variability and a history of unexpected episodes of neuroglycopenia. The change from 100 U/mL Lantus glargine to 300 U/mL Toujeo glargine insulin at the same dose occurred on Monday March 19th. Glycemic variability then subjectively reduced and the average daily interstitial glucose decreased to 170 mg/dL (9.4 mmol/L).

sometimes results in improvement of clinical signs, especially if the dose was high,[39] but often the outcome of insulin dose reduction is lower risk for hypoglycemia but persistence of poor diabetic control. Fluctuation between hyperglycemia and hypoglycemia often seems to follow a 3-day cycle.

- Availability of CGM has provided insight in humans with diabetes that was not possible from intermittent BG measurements. Individuals with increased glycemic variability present with poor diabetic control because of the occurrence of frequent hyperglycemia, whereas most of the hypoglycemic events are associated with no clinical signs and would be missed by standard intermittent BG monitoring. Nevertheless, the frequent hypoglycemia can induce physiologic unawareness of hypoglycemia and impaired glucose counterregulation, which in turn predisposes to increased risk of neuroglycopenia.[40] Whereas the periods of hypoglycemia are likely caused by excess exogenous insulin, the mechanisms for the periods of hyperglycemia are poorly understood and probably relate to the multiple causes of hyperglycemia and IR in DM.
- Longer-acting insulin preparations are generally recommended for treatment of DM in cats.[41–43] because they typically result in less potent and more prolonged duration of action than intermediate-acting products. Recently, a new 300 U/mL glargine insulin product (Toujeo) was shown to have a significantly longer and more flat time-action profile[44] than any other product, and early use in clinical cases has resulted in good outcomes.[45] Therefore, Toujeo glargine might provide benefit for cats with excessive glycemic variability.

Treatment and Outcome

- An Abbott Freestyle Libre flash glucose monitoring system was applied to side of the neck to provide more information on glucose excursions overnight and while Mu's owner was at work. The sensor was covered by a loose "scarf" around the neck (**Fig. 8**). Treatment with 1 U every 12 hours Lantus glargine insulin was continued. The owner compared interstitial and BG measurements whenever convenient. Marked glycemic variability was confirmed with glucose ranging less than 40 to greater than 400 mg/dL (<2.2 to >27.8 mmol/L) over the first 4 days (**Fig. 9**). No clinical signs caused by hypoglycemia were observed during this period.
- After 4 days, treatment was changed to 1 U every 12 hour of glargine 300 U/mL insulin administered with the prefilled Toujeo SoloStar pen (**Fig. 10**). Gradual smoothing out of the interstitial glucose curve was observed over the next 4 days (**Fig. 11**).
- Mu improved with resolution of PUPD and polyphagia over the first week. On two occasions during the first 6 weeks of treatment with Toujeo insulin, hypoglycemia with mild clinical signs occurred. The signs were much less severe than the owner was accustomed to so the episodes initially went unrecognized. The dose of Toujeo insulin was decreased first to 1 U every 24 hours and then to 1 U every 48 hours, and Mu then maintained good diabetic control on the latter dose with no further clinical signs of hypoglycemia for many months.

SUMMARY

Flash glucose monitoring allows frequent glucose monitoring in diabetic cats while avoiding patient discomfort, and therefore provides a useful tool in the management of diabetic cats, especially those with glycemic variability and/or in which glucose regulation is changing rapidly.

DISCLOSURE

The authors have nothing to disclose.

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