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ARTICLE TITLE

Updates in Feline Diabetes Mellitus and Hypersomatotropism

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The authors have nothing to disclose.

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Ketoacidosis, remission, acromegaly, glycemic variability

KEY POINTS

- Flash glucose monitoring is a useful addition to standard blood glucose monitoring and can provide frequent, non-invasive glucose measurements in a variety of settings.
- Hypophysectomy is the gold-standard treatment for hypersomatotropism-associated diabetes in cats and offers a good chance of cure of both hypersomatotropism and diabetes mellitus.

- Toujeo® insulin glargine appears to provide a more flat, constant activity profile than other long-acting insulins and could be particularly effective in cats with glycemic variability.

SYNOPSIS

Flash glucose monitoring is a novel, non-invasive monitoring technique, which is increasingly used in the management of small animal diabetes. This chapter provides guidance on the use of flash glucose monitoring in cats and demonstrates how this technique can be utilized in a range of feline diabetic cases, including those in which management is proving challenging. Other aspects of complicated feline diabetes cases are also discussed, including management of the sick diabetic cat, potassium depletion myopathy and treatment options for cats with hypersomatotropism-associated diabetes mellitus. The use of Toujeo® insulin glargine as a promising new long-acting insulin for diabetic cats is also discussed.

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, 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
- No other recent health concerns

Initial exam:

- 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^{o}C

TEXT BOX 1: Initial in-house clinical pathology results for Monkey

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

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

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

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

Plasma ALT: 107U/L (RI 20-100U/L)

Plasma ALP: 48U/L (RI 10-90U/L)

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

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

Plasma chloride: 110mEq/L (RI 110-126mEq/L) [110mmol/L (RI110-126mmol/L)]

Urine specific gravity: 1.023

Urine glucose: 4+

Urine ketones: 2+

Assessment:

- *Does this cat have DM or stress hyperglycemia?*

Presence of ketosis is useful to distinguish diabetic from non-diabetic sick cats and can be 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. Semi-quantitative blood/serum ketone measurement can be easily performed by applying a drop of serum or plasma to the ketone test patch of a urine dipstick, which provides a colorimetic 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 (DKA) 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 from 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 344mOsm/kg (Text Box 2). Patients are considered hyperosmolar at an osmolality >320mOsm/kg, whereas the more complicated Hyperosmolar Hyperglycemic State (HHS) is usually associated with osmolality >340 mOsm/kg and BG >600mg/dL (>33mmol/L).[6]

Therefore, Monkey should commence treatment for DKA and possible HHS. Treatment for 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 non-diabetic cats.[9]

TEXT BOX 2: Estimation of Plasma Osmolality

Estimated Osmolality (mOsm/kg) = $2*(Na^+ + K^+)$ + glucose(mg/dL)/18 + BUN(mg/dL)/2.8

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

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's solutions are commonly recommended.[6,10,11]
- A conservative fluid rate is recommended to avoid over-hydration and major osmotic shifts. Flow rates 1.5-2 times normal maintenance requirements (4-6mL/kg/hr) 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. As Monkey has an overweight body condition, it is prudent to use an estimation of ideal body weight (e.g. 5.5kg) for all dose calculations.
- Maintenance fluids should be supplemented with 30-40mEq/L (30-40mmol/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 due to anorexia, increased loss due to vomiting and diuresis. Fluid therapy causes dilution of circulating potassium concentrations and promotes further renal loss, while 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 above.

Insulin therapy:

- Insulin treatment should commence as soon as 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 will correct many metabolic derangements and cause BG to decrease, it won't 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, can be 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 can be substituted in CRI protocols as it has a similar action to regular insulin when delivered 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. Text Box 3 and Figure 1 provide a simple, "one size fits all" insulin CRI protocol that will be appropriate for Monkey.

- Protocols of repeated IM and SC injections are also effective. The most common protocol comprises an initial 0.2U/kg dose of regular insulin administered IM and followed with SC doses at 0.1U/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 0.25U/kg q12hrs. Blood glucose was checked q2-4hrs and the following actions taken:
    - 1 U regular insulin was administered q6hrs when BG was >250mg/dL (>14mmol/L)
    - 2.5% glucose CRI was given when BG was 80-250mg/dL (4.4-13.8mmol/L)
    - an IV bolus of glucose plus ongoing CRI with 5% glucose was given if BG was <80mg/dL (<4.4mmol/L).[20]

***TEXT BOX 3:* "One size fits all" insulin CRI protocol for sick diabetic cats**

- Add 25U (0.25mL) regular insulin to 500mL saline or lactated Ringer's solution (or 50U (0.5mL) to 1000mL solution), resulting in a 50mU/mL solution. Cover the fluid bag to protect insulin from light.
- Priming the line is unnecessary. Some insulin will adsorb 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 50mU/kg/hr is recommended, achieved by administering the above solution at 1mL/kg/hr (calculated using estimated ideal body weight).
- This rate is halved to 25mU/kg/hr (0.5mL/kg/hr of this solution) when BG reaches 180-270mg/dL (10-15mmol/L). At the same time, maintenance fluids should be changed to contain 2.5% dextrose in 0.45% saline supplemented with 30-40mEq/L (30-40mmol/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 25mU/kg/hr (0.5mL/kg/hr) with 2.5% dextrose in 0.45% saline

supplemented with potassium at 6mL/kg/hr. This is the safest option whenever close monitoring is not possible.

- Insulin infusion rate is adjusted up or down to maintain BG at 145-270mg/dL (8-15mmol/L). If the cat's illness is associated with substantial insulin resistance (IR), an insulin infusion rate of up to 150mU/kg/hr (3mL/kg/hr of the solution described above) may be required to maintain BG at 145-270mg/dL (8-15mmol/L).
- When a previously anorexic diabetic cat begins to eat, the IV insulin rate might need to be increased to manage increased glycemia.
- See Figure 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 <40mg/dL (<2.2mmol/L) or >400mg/dL (>22.2mmol/L). in this situation, blood glucose measurement can be performed if a more accurate result is required.
- The Abbott® Freestyle Libre® glucose monitoring system is an innovative and relatively 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 up to 8hrs (Figure 2). Whenever the sensor is scanned with the provided scanner, or smartphone App, a 'flash' of the current and previous 8hrs 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 will last up to 14 days, although sensor life is typically shorter in cats.

- Treatment decisions should not be based solely on interstitial glucose monitoring results. Instead, the Freestyle Libre® can identify changing glucose trends that can be 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 whilst also reducing staff workload. Text Box 4 provides tips for use of Freestyle Libre® flash glucose monitoring in sick diabetic cats.

TEXT BOX 4: Tips for use of Freestyle Libre® glucose monitoring in hospitalized diabetic cats

- A Freestyle Libre® glucose sensor should be applied as soon as 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 2mL/hr when the blood glucose is <270mg/dL (<15mmol/L)”. A technician can then periodically scan the sensor q1-2hrs without disturbing the cat and record the times and glucose results on the patient’s chart. Once interstitial glucose concentration decreases to <270mg/dL (<15mmol/L), this can be 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 q24hrs, 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 can be readily accessed by the veterinarian when reviewing overall progress.

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 12hrs and was discharged home after 24hrs with q12hr long-acting insulin therapy 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 both 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 1-2 days with full recovery within 2-3 weeks.[29]
- Monkey achieved diabetic remission that lasted for many years after 7 weeks of insulin treatment.
- The residual plantigrade gait presumably due to diabetic neuropathy gradually resolved by 3 months.
- He steadily lost weight and achieved an ideal body weight of 5.5kg after 5 months.

Case 2: CAT WITH HYPERSOMATOTROPISM-ASSOCIATED DM

Bonnie, 11 year old, female neutered, domestic longhair

Presentation

- DM diagnosed 4 months previously and treated with q12hr Lantus® insulin glargine since diagnosis
- Persistently poor glycemic control, despite increasing insulin dosage
- Obvious polyuria and polydipsia (PUPD), and extreme polyphagia. Overweight with minimal weight loss (200g) since diagnosis
- Currently receiving 10U (1.8U/kg) glargine q12hrs and fed a carbohydrate-restricted, wet commercial diet
- Recent serum fructosamine 680µmol/L (RI 249-320µmol/L)

- Home blood glucose measurements persistently >360mg/dL (>20mmol/l) throughout the day
- Presented for assessment of IR

Examination

- See Figures 3a and b for patient photograph and oral examination
- Weight: 5.5kg
- BCS: 6/9
- Muscle condition score: 2/3 (mild muscle loss)
- Alert, appropriate mentation
- Moderate hepatomegaly, mild prognathism inferior (Figure 2b). 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 (Text Box 5), but several features make hypersomatotropism (HS) a likely cause in Bonnie's case. Hypersomatotropism can cause particularly profound IR compared to other comorbidities, which is consistent with Bonnie's persistent, marked hyperglycemia, despite substantial insulin dosing. Extreme polyphagia, as seen in Bonnie, is a common finding in cats with HS.[30] Bonnie's subjective facial broadening and prognathism inferior (Figure 2a and 2b) suggest she is affected by acromegaly, which results from the mitogenic effects of excess growth hormone (GH). 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 relatively high reported prevalence of HS among diabetic cats. Hypersomatotropism has been estimated to cause approximately 25% of feline DM cases in the United Kingdom.[30] However, this could be an overestimation due to veterinarians' being more likely to submit samples for the study's free 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 insulin-like growth factor-1 (IGF-1) measurement was submitted and was supportive of HS (239nmol/L [1825ng/mL]; RI <130nmol/L [<1000ng/mL]).

TEXT 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

Are further diagnostic tests necessary to confirm HS?

A serum IGF-1 concentration of >130nmol/L (>1000ng/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 (CT) or, less often, magnetic resonance imaging (MRI) is often used to support the diagnosis by demonstrating pituitary enlargement. Despite this, 3-4% 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. Hypersomatotropism should therefore not be excluded based on a normal pituitary appearance on advanced imaging. Pituitary imaging also provides information which is relevant to several treatment modalities (Table 1).

What are the major treatment options for HS-associated DM?

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. Pre-operative cranial computer tomography revealed moderate pituitary enlargement (ventrodorsal height 8mm, normal ≤4mm[33]) (Figure 4). The extent of acromegalic cardiomyopathy was assessed pre-operatively using echocardiography in order to guide anesthesia and perioperative fluid therapy.

Pre-operatively, an Abbott® Freestyle Libre® flash glucose monitoring system was applied to provide frequent, non-invasive interstitial glucose measurement during the perioperative period (Figure 5). Hypophysectomy was performed via a transsphenoidal approach through the oral cavity (Figure 6).[34]

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 post-operatively, when long-acting maintenance insulin can be reintroduced. At the author's (RG) hospital, a maximum hourly rate of 4mL/kg/hr for all infusions is used to limit risk of volume overload. Cats often eat within 24hrs post-surgery. Insulin sensitivity can rapidly improve following successful surgery (Figure 7) so glucose concentration must be frequently monitored and insulin dose adjusted. Maintenance insulin is typically re-started at a reduced dose compared to pre-operatively due to improved insulin sensitivity.
- Treated cats require lifelong glucocorticoid and thyroxine supplementation due to 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 post-operatively until oral glucocorticoid therapy can be introduced. Oral levothyroxine is started once cats can tolerate oral medication.
- Antidiuretic hormone (ADH) supplementation is required at time of surgery and postoperatively to treat central diabetes insipidus because hypophysectomy causes cessation of ADH secretion by the neurohypophysis. Supplementation can eventually be discontinued in some cats because ADH 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 18hrs of surgery. Conjunctival desmopressin (1 drop q8hr) was started during surgery. Hydrocortisone CRI was replaced with oral hydrocortisone (0.5mg/kg q12hr) the day following surgery. Oral levothyroxine (0.1mg total dose q24hr) and a reduced dose of Lantus® glargine (3U q12hr) was introduced 2 days after surgery. Insulin sensitivity noticeably improved during post-operative hospitalization (Figure 7) and Bonnie was discharged 1 week post-surgery on a Lantus® glargine dose of 1U SC q12hr. Hydrocortisone dose was reduced to 0.5mg/kg q24hr at the time of discharge. One month post-operatively, IGF-1 measurement revealed resolution of hypersomatotropism (8.4nmol/L [64ng/mL]), and a serum total thyroxine measurement five hours post-pill was 55nmol/L (RI 19-65nmol/L) [4.3 µg/dL (RI 1.5-5.0µg/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 re-instated and continued at 1 drop q24hr indefinitely.

Case 3: EXCESSIVE GLYCEMIC VARIABILITY IN A DIABETIC CAT

Mu, 16 year old, neutered female Burmese

Presentation:

- DM 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.
- Insulin treatment was changed 9 months ago from veterinary porcine lente insulin (Vetsulin/Caninsulin®) administered q12hr with U-40 syringes to Lantus® glargine insulin administered q12hr with a Solostar® insulin dosing pen. Current dose is 1U q12h.

- BG monitoring at home is limited because the owner works long hours. In addition to occasional hypoglycemia, results over several months also frequently identified both moderate and severe hyperglycemia (range 30-685mg/dL, 1.7-38mmol/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: 4.7kg
- BCS: 6/9
- Muscle score: 3/3
- Mentation: Alert, appropriately responsive
- Unremarkable physical exam with a soft glossy coat.

Assessment:

- Several features of Mu's case are consistent with excessive "glycemic variability",[36] a condition which anecdotally appears to be more common in cats with long duration of DM.
- "Somogyi effect" is also often used to explain periods when both hypoglycemia and hyperglycemia occur. A more appropriate term which has been adopted in human 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 sometimes results in improvement of clinical signs, especially if the dose was relatively 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 appears to follow a 3-day cycle.
- Availability of CGM has provided insight in human diabetics that was not possible from intermittent BG measurements. Individuals with increased glycemic variability present with poor diabetic control due to 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 counter-regulation, which in turn predisposes to increased risk of neuroglycopenia.[40] Whereas the periods of hypoglycemia are likely caused by excess exogenous insulin, the mechanism(s) 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 300U/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 very 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 (Figure 8). Treatment with 1U q12hr Lantus® glargine insulin was continued. The owner compared interstitial and blood glucose measurements whenever convenient. Marked glycemic variability was confirmed with glucose ranging <40 to >400mg/dL (<2.2 to >27.8mmol/L) over the first 4 days (Figure 9). No clinical signs due to hypoglycemia were observed during this period.
- After 4 days, treatment was changed to 1U q12h glargine 300 U/mL insulin administered with the pre-filled Toujeo® SoloStar® Pen (Figure 10). Gradual smoothing out of the interstitial glucose curve was observed over the next 4 days (Figure 11).
- Mu improved with resolution of PUPD and polyphagia over the first week. On 2 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 1U q24hr and then to 1U q48hr, 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.

1. Zeugswetter F, Handl S, Iben C, Schwendenwein I. Efficacy of plasma beta-hydroxybutyrate concentration as a marker for diabetes mellitus in acutely sick cats. *Journal of feline medicine and surgery.* 2010;12(4):300-305.
2. Zeugswetter F, Pagitz M. Ketone measurements using dipstick methodology in cats with diabetes mellitus. *The Journal of small animal practice.* 2009;50(1):4-8.
3. Chong SK, Reineke EL. Point-of-Care Glucose and Ketone Monitoring. *Top Companion Anim Med.* 2016;31(1):18-26.
4. Di Tommaso M, Aste G, Rocconi F, Guglielmini C, Boari A. Evaluation of a portable meter to measure ketonemia and comparison with ketonuria for the diagnosis of canine diabetic ketoacidosis. *J Vet Int Med.* 2009;23(3):466-471.
5. ESVE. Project ALIVE. https://www.esve.org/alive/search.aspx. Accessed Jan 4, 2020.
6. Davison LJ. Diabetic ketoacidosis, ketoacidosis, and the hyperosmolar syndrome. In: Feldman EC, Fracassi F, Peterson ME, eds. *Feline Endocrinology*. Milano, Italy: Edra; 2019:454-467.
7. Callegari C, Mercuriali E, Hafner M, et al. Survival time and prognostic factors in cats with newly diagnosed diabetes mellitus: 114 cases (2000-2009). *Journal of the American Veterinary Medical Association.* 2013;243(1):91-95.
8. Sieber-Ruckstuhl NS, Kley S, Tschuor F, et al. Remission of diabetes mellitus in cats with diabetic ketoacidosis. *J Vet Int Med.* 2008;22(6):1326-1332.
9. Zini E, Benali S, Coppola L, et al. Renal morphology in cats with diabetes mellitus. *Veterinary pathology.* 2014;51(6):1143-1150.
10. Rudloff E. Diabetic ketoacidosis in the cat: recognition and essential treatment. *Journal of feline medicine and surgery.* 2018;19(11):1167-1174.
11. Thomovsky E. Fluid and Electrolyte Therapy in Diabetic Ketoacidosis. *The Veterinary clinics of North America Small animal practice.* 2017;47(2):491-503.
12. Jayashree M, Williams V, Iyer R. Fluid Therapy For Pediatric Patients With Diabetic Ketoacidosis: Current Perspectives. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy.* 2019;12:2355-2361.
13. DiFazio J, Fletcher DJ. Retrospective comparison of early- versus late-insulin therapy regarding effect on time to resolution of diabetic ketosis and ketoacidosis in dogs and cats: 60 cases (2003-2013). *J Vet Emerg Crit Care (San Antonio).* 2016;26(1):108-115.
14. Cooper RL, Drobatz KJ, Lennon EM, Hess RS. Retrospective evaluation of risk factors and outcome predictors in cats with diabetic ketoacidosis (1997-2007): 93 cases. *J Vet Emerg Crit Care (San Antonio).* 2015;25(2):263-272.
15. Malerba E, Mazzarino M, Del Baldo F, et al. Use of lispro insulin for treatment of diabetic ketoacidosis in cats. *Journal of feline medicine and surgery.* 2019;21(2):115-123.
16. Pipe-Martin HN, Fletcher JM, Gilor C, Mitchell MA. Pharmacodynamics and pharmacokinetics of insulin aspart assessed by use of the isoglycemic clamp method in healthy cats. *Domestic animal endocrinology.* 2018;62:60-66.
17. Scholtz HE, Pretorius SG, Wessels DH, Venter C, Potgieter MA, Becker RH. Equipotency of insulin glargine and regular human insulin on glucose disposal in healthy subjects following intravenous infusion. *Acta Diabetol.* 2003;40(4):156-162.
18. Feldman EC, Nelson RW, Reusch C, Scott-Moncrieff. *Canine and Feline Endocrinology, 4th Edition.* Saunders; 2014.
19. Marshall RD, Rand JS, Gunew MN, Menrath VH. Intramuscular glargine with or without concurrent subcutaneous administration for treatment of feline diabetic ketoacidosis. *J Vet Emerg Crit Care (San Antonio).* 2013;23(3):286-290.
20. Gallagher BR, Mahoney OM, Rozanski EA, Buob S, Freeman LM. A pilot study comparing a protocol using intermittent administration of glargine and regular insulin to a continuous

rate infusion of regular insulin in cats with naturally occurring diabetic ketoacidosis. *Journal of Veterinary Emergency and Critical Care.* 2015;25(2):234-239.
21. Kang MH, Kim DH, Jeong IS, Choi GC, Park HM. Evaluation of four portable blood glucose meters in diabetic and non-diabetic dogs and cats. *Vet Q.* 2016;36(1):2-9.
22. Zini E, Moretti S, Tschuor F, al. e. Evaluation of a new portable glucose meter designed for the use in cats. *Schweizer Archiv fur Tierheilkunde.* 2009;151(9):448-451.
23. Cohen TA, Nelson RW, Kass PH, Christopher MM, Feldman EC. Evaluation of six portable blood glucose meters for measuring blood glucose concentration in dogs. *Journal of the American Veterinary Medical Association.* 2009;235(3):276-280.
24. Reineke EL, Fletcher DJ, King LG, G. L, Drobatz KJ. Accuracy of a continuous glucose monitoring system in dogs and cats with diabetic ketoacidosis. *Journal of Veterinary Emergency and Critical Care.* 2010;20(3):303-312.
25. Moretti S, Tschuor F, Osto M, et al. Evaluation of a novel real-time continuous glucose-monitoring system for use in cats. *J Vet Int Med.* 2010;24(1):120-126.
26. Dietiker-Moretti S, Muller C, Sieber-Ruckstuhl N, et al. Comparison of a continuous glucose monitoring system with a portable blood glucose meter to determine insulin dose in cats with diabetes mellitus. *J Vet Int Med.* 2011;25(5):1084-1088.
27. Fleeman LM. Flash glucose monitoring in diabetic dogs and cats. Paper presented at: American College of Veterinary Internal medicine Forum 2019; Phoenix AZ, USA.
28. Feldman EC, Church DB. Electrolyte disorders: Potassium (Hyper/Hypokalemia). In: Ettinger SJ, Feldman EC, eds. *The textbook of veterinary internal medicine*. 7th ed: Saunders Elsevier; 2010:303-307.
29. Dow SW, Fettman MJ. Management of potassium-depleted cats. *Compendium on Continuing Education for the Practising Veterinarian.* 1990;12:1612-1615.
30. Niessen SJ, Forcada Y, Mantis P, et al. Studying Cat (Felis catus) Diabetes: Beware of the Acromegalic Imposter. *PloS one.* 2015;10(5):e0127794.
31. Lamb CR, Ciasca TC, Mantis P, et al. Computed tomographic signs of acromegaly in 68 diabetic cats with hypersomatotropism. *Journal of feline medicine and surgery.* 2014;16(2):99-108.
32. Schaefer S, Kooistra HS, Riond B, et al. Evaluation of insulin-like growth factor-1, total thyroxine, feline pancreas-specific lipase and urinary corticoid-to-creatinine ratio in cats with diabetes mellitus in Switzerland and the Netherlands. *Journal of feline medicine and surgery.* 2017;19(8):888-896.
33. Tyson R, Graham JP, Bermingham E, Randall S, Berry CR. Dynamic computed tomography of the normal feline hypophysis cerebri (Glandula pituitaria). *Vet Radiol Ultrasound.* 2005;46(1):33-38.
34. Meij BP, Voorhout G, Van Den Ingh TS, Rijnberk A. Transsphenoidal hypophysectomy for treatment of pituitary-dependent hyperadrenocorticism in 7 cats. *Vet Surg.* 2001;30(1):72-86.
35. Owen TJ, Martin LG, Chen AV. Transsphenoidal Surgery for Pituitary Tumors and Other Sellar Masses. *The Veterinary clinics of North America Small animal practice.* 2018;48(1):129-151.
36. Zini E, Salesov E, Dupont P, et al. Glucose concentrations after insulin-induced hypoglycemia and glycemic variability in healthy and diabetic cats. *J Vet Int Med.* 2018;32(3):978-985.
37. Service FJ. Glucose variability. *Diabetes.* 2013;62(5):1398-1404.
38. Gilor C, Fleeman LM. The Somogyi effect: Is it clinically significant? . American College of Veterinary Internal Medicine Forum; 2017; National Harbor, MD, USA.
39. McMillan FD, Feldman EC. Rebound hyperglycemia following overdosing of insulin in cats with diabetes mellitus. *Journal of the American Veterinary Medical Association.* 1986;188(12):1426-1431.
40. Fanelli CG, Porcellati F, Pampanelli S, Bolli GB. Insulin therapy and hypoglycaemia: the size of the problem. *Diabetes/metabolism research and reviews.* 2004;20 Suppl 2:S32-42.

41. Sparkes AH, Cannon M, Church D, et al. ISFM Consensus Guidelines on the Practical Management of Diabetes Mellitus in Cats. *Journal of feline medicine and surgery.* 2015;17(3):235-250.
42. Behrend E, Holford A, Lathan P, Rucinsky R, Schulman R. 2018 AAHA Diabetes Management Guidelines for Dogs and Cats. *Journal of the American Animal Hospital Association.* 2018;54(1):1-21.
43. Thompson A, Lathan P, Fleeman L. Update on insulin treatment for dogs and cats: insulin dosing pens and more. *Vet Med (Auckl).* 2015;6:129-142.
44. Gilor C, Culp W, Ghandi S, do Carmo Emidio ESJA, Ladhar A, Hulsebosch S. Comparison of pharmacodynamics and pharmacokinetics of insulin degludec and insulin glargine 300 U/mL in healthy cats. *Domestic animal endocrinology.* 2019;69:19-29.
45. Linari G, Gilor C, Fleeman LM, Fracassi F. Insulin glargine 300U/mL for the treatment of diabetes mellitus in cats [abstract]. 30th ECVIM-CA Congress; 2020; Barcelona.
46. Wormhoudt TL, Boss MK, Lunn K, et al. Stereotactic radiation therapy for the treatment of functional pituitary adenomas associated with feline acromegaly. *J Vet Int Med.* 2018;32(4):1383-1391.
47. Dunning MD, Lowrie CS, Bexfield NH, Dobson JM, Herrtage ME. Exogenous insulin treatment after hypofractionated radiotherapy in cats with diabetes mellitus and acromegaly. *J Vet Int Med.* 2009;23(2):243-249.
48. Mayer MN, Greco DS, LaRue SM. Outcomes of pituitary tumor irradiation in cats. *J Vet Int Med.* 2006;20(5):1151-1154.
49. Kenny P, Scudder CJ, Keyte S, et al. Treatment of feline hypersomatotropism - efficacy, morbidity and mortality of hypophysectomy [abstract]. *J Vet Int Med.* 2015;29:1271.
50. Abrams-Ogg AC, Holmberg DL, Stewart WA, Claffey FP. Acromegaly in a cat: Diagnosis by magnetic resonance imaging and treatment by cryohypophysectomy. *Can Vet J.* 1993;34(11):682-685.
51. Blois SL, Holmberg DL. Cryohypophysectomy used in the treatment of a case of feline acromegaly. *The Journal of small animal practice.* 2008;49(11):596-600.
52. Gostelow R, Scudder C, Keyte S, et al. Pasireotide Long-Acting Release Treatment for Diabetic Cats with Underlying Hypersomatotropism. *J Vet Int Med.* 2017;31(2):355-364.
53. Scudder C, Hazuchova K, Gostelow R, et al. Pilot study assessing the use of cabergoline in the management of diabetic acromegalic cats [abstract]. *J Vet Int Med.* 2018;32:552.

Figure Legends

Figure 1: Example of a fluid therapy flow chart for use in hospitalized diabetic cats. Diagram author's (LF's) own.

Figure 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).

Figure 3: Patient photographs demonstrating subjectively broad facial features (a) and prognathism inferior (b).

Figure 4: Transverse cranial computed tomography image showing pituitary enlargement.

Figure 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.

Figure 6: Patient is positioned (prior to draping) for transsphenoidal hypophysectomy

Figure 7: Interstitial glucose curves, generated using a flash CGM system, before (a) and 5 days' after (b) hypophysectomy, showing greatly improved insulin sensitivity (images courtesy of Dr. J. Cockerill, Eaton Bunbury Veterinary Clinic, permission obtained July 26th 2019)

Figure 8: A loose 'scarf' (middle and right) can protect a flash CGM 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.

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

Figure 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 to draw the 300 U/mL insulin from the dosing pen using a syringe.

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

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 e.g. acromegalic changes - DM control often poor with severe ongoing DM signs - Large insulin doses potentially required, which can be 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 so improve any neurological signs **Disadvantages** - Typically weeks-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)
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** - Very 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
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 5-10µg/kg PO SID.[53] Further research warranted.