

## FELINE DIABETES UPDATE: INSIGHTS IN DIAGNOSIS AND MANAGEMENT

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Diabetes mellitus is one of the two most common endocrine disorders in cats. It is a heterogeneous group of disorders in which insulin production is reduced or in which tissue cells are resistant to the effects of insulin, resulting in impaired glucose homeostasis. From a clinical perspective, regardless of the cause, diabetes mellitus (DM) can be challenging to diagnose and treat in the cat because of their stress-induced hyperglycemia.

The prevalence of this condition has increased over time from 8 out of 10,000 (in 1970) to 124 of 10,000 (in 1999) cats seen at veterinary teaching hospitals (Prahl). The frequency of occurrence also appears to vary with geographic location (0.21% in Swedish cats (Sallander); 0.43% in the United Kingdom (McCann); 0.74% of Australian cats (Lederer 2009)), with British and Australian Burmese being significantly over-represented at 3.7 and 3-fold, respectively. Fasting glucose concentrations are higher and glucose tolerance is lower in Burmese cats in Australia, New Zealand and the UK compared to matched non-Burmese cats (Lederer 2005). It appears to be inherited as an autosomal, not fully penetrant trait in these Burmese (O'Leary).

### **PATHOPHYSIOLOGY REVIEW**

Insulin is secreted after a meal, to facilitate utilization and storage of glucose, fat and amino acids in three primary tissues: liver, muscle and fat. A mild insulin deficiency results in decreased transfer of ingested nutrients into tissues causing mild to moderate hyperglycemia. Severe insulin deficiency not only hampers tissue uptake of ingested fuels, but also results in marked compensatory glucose overproduction along with excessive mobilization of the body's protein and fat stores. Combined with glucagon excess (relative or absolute), this results in an increased delivery of fatty acids to the liver, their oxidation to ketone bodies (beta-hydroxy-butyrate, acetoacetate, and acetone), and a clinical state of ketoacidosis. Because there is no insulin available to deliver the glucose into the cells, cells starve and polyphagia with concurrent weight loss occurs. Unabsorbed glucose (hyperglycemia) spills into the urine drawing water with it. This causes polyuria and compensatory polydipsia.

### ***Classification and Differentiation Between Type 1 and Type 2 Diabetes***

In human diabetes, Type 1 refers to a condition of insulin dependency seen in people who are generally lean, young and prone to ketogenesis. It is caused by immune-mediated beta cell depletion, causing an absolute insulin deficiency. Type 2 DM usually occurs in the older human, often obese but less prone to the development of ketoacidosis. The underlying problem is one of insulin receptor and post receptor defects, interfering with insulin uptake by tissues. This insulin resistance, and associated hyperglycemia, causes the beta cells to produce more insulin, thus this state is one of a relative insulin deficiency. Type 2 may be controlled, at least initially, with weight loss, diet and oral hypoglycemic agents.

Generally, diabetes is a disorder of the older, often overweight cat, similar to Type 2 diabetes in humans. Risk factors include body weight > 7 kg, older age (> 10 years), male gender, neutered. Hensho showed that increased body condition score (BCS) in nondiabetic cats is associated with increased circulating concentrations of IAPP and insulin. Obese cats appear to have a defect in insulin secretion along with lower tissue sensitivity to insulin. Unlike human Type 2, however, by the time the diagnosis of diabetes is made, most cats are insulin dependent although not prone to ketogenesis. In addition to these differences, cats may also develop diabetes secondary to endocrinopathies (acromegaly or hyperadrenocorticism), or drug therapy (glucocorticoids and progestins). Inflammation is another recognized predisposing factor for susceptible individuals to develop diabetes. Franchini has shown at a molecular level that the inflammation induced by bacterial or viral infection can, via molecules recognized by toll-gate receptors, damage endocrine pancreatic tissue. It remains unclear whether pancreatitis is a significant co-morbidity (Forcada) or whether it may be a) a source of inflammation no different than other sites or b) pancreatitis develops as a result of beta cell apoptosis.

Additionally, in cats, pancreatic islet amyloid deposits are believed to interfere with insulin secretion, and that oral hypoglycemics (such as the secretagogue sulfonylureas) may actually increase islet amyloid polypeptide (IAPP) deposition. IAPP is co-secreted with insulin. Islet amyloidosis occurs in 90% of humans with Type 2 DM. (O'Brien)

Thus, feline diabetes shares several similarities with the disease in humans. Impaired beta cell function, decreased beta cell mass, insulin resistance that is often related to obesity, and pancreatic amyloid deposition, are among these common features. (Zini March 2010) Unlike humans, DM does not predispose cats to hypertension.

## **DIAGNOSIS**

In the stressed patient, epinephrine release causes hyperglycemia and glucosuria. Therefore, even in cats with history and clinical findings of polyuria/polydypsia, polyphagia, weight loss, hyperglycemia and glucosuria, it is essential to differentiate between this stress response and diabetes. This can be done through verifying that the hyperglycemia and glucosuria are persistent over time. However, because stress recurs a better option is to request that a fructosamine level be run on the previously collected sample. Fructosamine measures the protein bound glucose levels over the preceding 10 - 20 days. It can be affected by protein metabolism as well, hence hyperthyroidism, with more rapid muscle turnover, may result in artificially lower fructosamine values. Glycohemoglobin A1c reflects glycemic control from the previous 70 days.

Urine ketone measurement is routinely performed in cats with diabetes mellitus to identify impending or established ketoacidosis. The urinary ketone dipstick test has a low sensitivity as it quantifies the less abundant ketone acetoacetate. Beta-hydroxybutyrate (beta-OHB) is the predominant serum ketone. Determination of plasma beta-OHB concentration was shown to be a useful method to distinguish between diabetic and non-diabetic sick cats. (Zeugswetter)

## **THERAPY AND MANAGEMENT OF THE DIABETIC CAT**

### ***Remission***

Reversal of the diabetic state is appealing; some believe that it should be the goal of insulin therapy. (Roomp, Marshall) In some papers, remission is reported to occur in over 80% of newly diagnosed diabetic cats, when tight glycemic control is initiated early after diagnosis. Good glycemic control soon after diagnosis is associated with increased probability of remission. In the same studies, approximately 25-30% of cats in remission relapse, and require further insulin therapy to control blood glucose. These cats have impaired glucose tolerance, with 19% having impaired fasting blood glucose. A study presented in 2015 showed that 20 diabetic cats in remission (as defined by 2 weeks without insulin) had a range of metabolic disturbances: decreased glucogenic amino acids and increased urea.

In a study published in 2010, clinical remission of diabetes was evaluated. Ninety cats with newly diagnosed diabetes were followed until death or remission. Remission was defined as normoglycemia without insulin for  $\geq 4$  weeks. Likelihood of remission was found to be greater in older cats and in cats with higher body weight. Remission was less likely in cats with increased serum cholesterol and was of shorter duration when serum glucose was higher, i.e., less well regulated. (Zini, Nov 2010).

In a systematic review of feline diabetic remission by Gostelow et al (2014), the level of evidence for remission was found to be moderate to poor due to several factors. These included the lack of randomization and blinding in trials, and small sample size. Additionally, a critical flaw was the general failure to provide criteria for the diagnosis of diabetes or diabetic remission. Finally, confounding factors were not controlled for or excluded.

In a one-year prospective randomized trial comparing efficacy of glargine and PZI in 46 newly diagnosed diabetic cats. All had been transitioned to a low carbohydrate diet 10 days before starting insulin. Overweight cats were assigned caloric intake of the same diet designed for weight loss. No differences were seen in any parameters between glargine and PZI treated cats. Eight (33%) of glargine-treated cats and 5 (23%) of PZI-treated cats achieved remission. Using univariate analysis, baseline body weight, ( $>5.2$ kg), baseline body mass index ( $\geq 25$  %), and weight loss at the 1 month time point were identified as parameters possibly associated with remission; a minimum of 2% weight loss at the one month time point was the only significant predictor of remission. (Gostelow, 2017a)

Additionally, Gostelow et al performed a retrospective cohort study aiming to determine occurrence and risk factors associated with remission in newly diagnosed diabetic cats seen in 103 primary care practices in the United Kingdom over a 5-year period. Data was collected regarding 583 cats.

- 347 male, 235 female, 1 unknown
- 517 (88.2%) mixed breed, 24 (4.1%) Burmese
- Median age = 13 years, median weight 4.5 kg
- Median follow-up time 232 days (42-596)

Remission was defined as “lack of DM-related clinical signs, +/- a recorded blood glucose < 10 mmol/L (<180mg/dl), for at least 28 days after discontinuation of all antihyperglycemic therapy (excluding prescription DM diet)”. One-year cumulative probability of remission was 13.1%. Factors that were found to be independently predictive of remission were glucocorticoid therapy in the 90 days before diagnosis and/or Burmese breed. Survival longer than 30 days past diagnosis was reduced in cats not receiving anti-hyperglycemic therapy and/or having a low body weight. (Gostelow, 2017b)

### **Oral therapy**

In December 2022, bexagliflozin (Bexacat) has been approved by the FDA as the first oral treatment for cats with diabetes mellitus. This compound is a sodium-glucose cotransporter 2 (SGLT2) inhibitor that works by preventing renal tubules from reabsorbing glucose. Thus, rather than being hyperglycemic, the glucose is passed in urine (Hoenig, Gal). This drug is only suitable for cats that are still making insulin and are not dependent on exogenous insulin. Bexagliflozin does not replace insulin and does not improve glucose uptake by cells, it merely decreases hyperglycemia. Therefore, cats may be at greater risk for diabetic ketoacidosis (DKA) as well as euglycemic DKA. It should not be used in cats with decreased renal function (chronic kidney disease). There is no evidence that cats on this drug are predisposed to urinary tract infections. The literature on use of this agent in cats is sparse (Benedict), but anecdotally, veterinary endocrinologists (VIN) are optimistic that bexagliflozin will be of great benefit for cats however it will be a while before we know which cats are the best candidates and how best to use it in them.

### **Insulin Type**

There are many types of insulin available: they are derived from several sources and have several durations of action. All insulins approved for humans are currently produced from human recombinant technology. However, beef-pork and beef sourced insulins may be better suited to cats because of closer structural similarity to feline insulin.

Speed of Onset and Duration: The speed, onset of action and duration differs between insulins.

1. Regular (fast) - rapid onset of action (0.5h), max. effect (1-5h), end effect (8h)
2. NPH (intermediate) - onset of action (1.5h), max. effect (4-12h), end effect (24h)
3. Lente - onset of action (2.5h), max. effect (7-15h), end effect (24h)
4. Semilente - onset of action (1.5h), max. effect (5-10h), end effect (16h)
5. Combination: 70% NPH: 30% regular - onset of action (0.5h), max. effect (4-8h), end effect (24h)
6. Ultralente (long acting) - onset of action (4h), max. effect (10-30h), end effect (36h)
7. Synthetic insulin analogues: glargine and detemir (ultra-long acting) once a day in humans

These values are for comparison only and reflect human metabolism. Insulin responses vary with the individual. Every cat is different and will respond differently to the insulin they take in the management of diabetes. It is ALWAYS advisable to follow therapeutic decision cascade and start with an insulin that is licenced for veterinary use. Remember too that an individual's response may change over time. Diabetes is a dynamic process.

Vetsulin™/Caninsulin™, is a 40 U/ml porcine lente zinc insulin specifically registered for veterinary use. It has been available for several decades as Caninsulin and is known as Vetsulin™ in the United States. Its peak activity is ~3h and duration of 6-10h. It is very effective for the treatment of many cats with diabetes.

Protamine zinc insulin (PZI) is a long-acting, beef-pork insulin that was considered by many to be the insulin of choice for cats because of its molecular similarity to feline insulin. Since November 2009, an FDA approved recombinant human protamine zinc insulin preparation, ProZinc™, has come on the veterinary market. Like Vetsulin™/Caninsulin™, it is a 40 unit/ml (U 40) insulin.

Humulin N and Novolin N are recombinant human NPH insulins (100 U/ml) that have an intermediate duration of

action. They do not work well in most cats.

Glargine (Lantus™) is a long-acting human recombinant DNA insulin analogue that has been modified by replacing one amino acid (asparagine) with another (glycine) as well as adding 2 arginine amino acids to the c-terminal end of the molecule. This changes the pH solubility making it microprecipitate at the site of subcutaneous injection that are slowly absorbed. This should result in fewer troughs and a slower, smoother glycemic effect, however this does not appear to occur in all cats. Because the formation of microcrystals and slow absorption are dependent on the acidity of the product, glargine cannot be mixed or diluted.

Interestingly, in cats with diabetic ketoacidosis, glargine may be used in place of regular (Toronto) insulin if given IM or IV. By these routes, it has a similar action profile to that of regular insulin. In fact, in some resistant diabetic cats, one might consider using it by both the IM and SC routes BID with 70% of the dose given SC and 30% of the dose given IM. Intravenous Lispro insulin via constant rate infusion (CRI) and physiologic saline have been shown to be safe and effective in a small study of cats with DKA when compared to a CRI of Regular insulin and saline (Anderson).

Detemir (Levemir™) is another long-acting human rDNA analogue. It is modified from insulin by adding an acylated fatty acid chain. This allows reversible binding to plasma proteins, resulting in a slow release into plasma. In cats, its action and duration are similar to those of glargine. The dose required may be less than that of glargine (~30% less in the Gilor study). Remission rates and time to remission are similar.

Newer Insulin Analogues: Rapid-acting insulin analogues lispro, aspart, and glulisine act by blocking the formation of insulin dimers and hexamers. This allows larger amounts of the active monomeric insulin to be immediately available for postprandial use when given at mealtime. Studies in dogs and cats have yet to be reported.

Insulin degludec (Tresiba™) is a new-generation, ultra-long-acting analogue not yet available in North America or Europe. It forms large soluble multi-hexamers at the injection site. It has an extremely long action in humans (given once daily or three times a week). In a small study of 6 healthy cats that compared degludec to PZI, there was no difference in duration of action between the insulins when both were given at 0.3 IU/kg, However, when the cats received 0.1 or 0.2 IU/kg of either insulin, the median duration of action was significantly longer for degludec (7 vs. 11h and 6.8 vs 12.5h, respectively). Time to nadir, nadir value and onset of action did not differ between the two insulin types at the same dose (Salesov).

A concept not widely used in veterinary medicine that may help with some difficult diabetics is that of combining insulins to have one that provides basal control and another covering mealtime glycemic needs (basal-bolus therapy). In humans, this approach is taken using premixed combinations of a short-acting and a longer-acting or ultra-long-acting insulin analogues. While not yet studied in cats (or dogs), this effect might be achieved through giving SC glargine concurrently with an IM dose BID or by using SC Caninsulin/Vetsulin or ProZinc concurrently with SC glargine or detemir BID. The insulins must not be mixed in one syringe.

### ***Insulin Concentration***

It is critical to know the concentration of the insulin you are using and to match the syringes to that strength. For correct dosing, insulin should be administered using syringes specifically calibrated for the strength of insulin used. For example, most insulin is 100 Units/ml (U100) and micro-fine or ultra-fine U100 syringes should be used with these. With U-100 insulin, when only small amounts of insulin are needed, using a 3/10cc or 5/10cc U-100 allows even the tiniest dose to be measured more accurately.

The advantage of using a 40 unit/ml insulin is that it is easier to more accurately dose small amounts of insulin. The specific U-40 syringes should be prescribed with this product. As the use of U100 syringes for a more dilute U40 insulin risks miscommunication and tragic consequences.

While there are guidelines in choosing the starting dose of insulin for a patient, the maximum dose for that patient is the dose that he/she needs to resolve the clinical signs of excessive urination and drinking, lethargy and weakness. The majority of cats require twice daily injections, regardless of the type of insulin selected.

### **DIFFERENTIALS FOR THE DIFFICULT TO CONTROL DIABETIC**

The biggest cause for poor glycemic control is lack of compliance or failure of comprehension regarding insulin handling. Reviewing aspects of injection technique, watching the client draw up and administer insulin may reveal the problem. Some disorders mimic uncontrolled diabetes (e.g., chronic kidney disease, hyperthyroidism, lower pollakiuria of lower urinary tract disorders, and PU/PD of hypercalcemia). Others cause insulin resistance. These include obesity, untreated infectious or inflammatory conditions (e.g., dental disease, lower urinary tract infection, inflammatory bowel disease, asthma, pancreatitis). Attempts to identify and ameliorate them through appropriate therapy (including antimicrobials or glucocorticoids as needed) will be helpful. Iatrogenic resistance induced in some individuals through exposure to progestational substances (e.g., glucocorticoids, megestrol acetate, progesterone). Neoplastic or hyperplastic conditions (e.g., hyperadrenocorticism, hyperprogesteronemia, hyperaldosteronemia, acromegaly) may interfere with control.

### **ACROMEGALY**

The primary differentials for insulin resistance or uncontrolled diabetes include treatment failure of compliance or comprehension, inappropriate insulin handling, resistance associated with concurrent, uncontrolled inflammatory or infectious conditions. Neoplasia (HAC, hyperprogesteronemia, and acromegaly) should not be considered until these have been ruled out.

Acromegaly has been reported to occur in 18-25% of diabetic cats seen in tertiary care institutions in Europe and the UK. Caused by pituitary adenoma or hyperplasia, increased secretion of growth hormone (somatostatin) causes post receptor defects resulting in catabolic and diabetogenic effects. These last are due to increased hepatic insulin-like growth factor (IGF-1) release. IGF-1 has anabolic effects that affect the musculoskeletal system (prognathism, thickened limbs, clubbed paws, arthropathy, upper respiratory stridor) and organomegaly (cardiac hypertrophy, renomegaly). Pituitary enlargement may result in neurologic signs in some individuals.

Diagnosis is made through measurement of IGF-1 with confirmation by imaging of the pituitary gland. Ideally, growth hormone (GH) is measured. Because GH is secreted in a pulsatile manner, there may be false negatives, i.e., normal GH values in an acromegalic cat. IGF-1 is more reliable because it is secreted continuously. Contrast enhanced CT or MRI studies are used for diagnosis as well as for treatment planning, should radiation or stereotactic radiosurgery be a consideration.

Traditionally, treatment has been conservative (i.e., increased doses of insulin as needed), surgery (transsphenoidal hypophysectomy, or radiation to reduce pituitary mass. Identification of the somatostatin receptor types (SSTR 1, SSTR 2, and SSTR 5) offers hope that the long-acting somatostatin multireceptor-binding analogue pasireotide may provide relief. (Gostelow 2017, Scudder 2016)

Regardless of form of therapy, the effects of IGF-1 (arthropathies, cardiomyopathy, CKD and hypertension) must be addressed to optimize quality of life.

### **CLIENT COUNSELLING**

Once the cat has been determined to be diabetic, client counselling is very important. Initially, most clients are intimidated at the thought of administering insulin injections. Booking a discharge or demonstration appointment with the nurse-technologist works well, as nurses are often more patient than veterinarians are at explaining and guiding the learning client.

At this appointment, review the pertinent facts about insulin storage (away from heat and refrigerate after first dose removed), handling (gently), re suspension (roll of shake), drawing up into the syringe or priming the pen, administration (upon exhalation of client, walk through the door of the tent, OR pull the tent over the needle,

think canvas, practise on a cat using saline), single use only of insulin syringes for sterility and sharpness and how long to use the vial or cartridge.

Show the client how to keep a diary, recording date, time of insulin administration, dose administered, activity level, BM, amount urinated (# and size of clumps of clumping litter), amount eaten, and amount drunk (by difference, measure amount left in bowl the next morning).

Counsel on diet to be fed, as determined by the veterinarian. Lower carbohydrate, higher protein diets may be more effective for glycemic control, however this remains controversial. There is no scientific consensus on carbohydrates: to date there is no clear evidence that carbohydrates either cause or are contraindicated in the treatment of feline diabetes (Farrow, Coradini, Sallander, Slingerland, Owens, Hoenig). The native diet for a cat (bird or mouse) is high protein, moderate fat, low carbohydrate, it is reasonable to feed this macronutrient profile for any cat. Cats should have free access to food all the time, rather than feeding twice daily.

Some cats refuse to eat the diets we recommend. For those patients and for clients unwilling/unable to offer those diets, here is a website which lists the protein and carbohydrate proportions of grocery store brands: [www.catinfo.org/docs/CatFoodProteinFatCarbPhosphorusChart.pdf](http://www.catinfo.org/docs/CatFoodProteinFatCarbPhosphorusChart.pdf). Other helpful websites for clients to use for information, support and encouragement (including teaching techniques) follow:

[www.petdiabetes.com](http://www.petdiabetes.com), [www.felinediabetes.com](http://www.felinediabetes.com), Vetsulin/Caninsulin: <http://www.cat-dog-diabetes.com/>, and ProZinc: <https://prozinc.us/cat-owners/prozinc-video-library>.

Cats with comorbidities that require a different diet should be fed the diet appropriate for their concurrent disease. Insulin dose can be regulated with consistent feeding of any diet. Similarly, should a diabetic cat need prednisolone for a concurrent problem (e.g., asthma or inflammatory bowel disease (IBD)), treat the underlying problem as needed and regulate the insulin to that corticosteroid dose. If the antiinflammatory action can be provided through a non-glucocorticoid agent, (e.g., chlorambucil for IBD, an NSAID for arthritis), then that can be attempted.

Monitoring urine parameters at home is justified for:

- Cats with transient diabetes- to identify when/if glucosuria recurs
- Cats on oral hypoglycemics to determine if glucosuria resolves
- Cats previously or currently ketoacidotic - to monitor for ketones

### **FOLLOW-UP CARE AND MONITORING**

At the discharge time, book an appointment for a blood glucose curve and re-evaluation for 14 days later. Let the client know that you will call daily for the first 3 - 4 days, to be supportive and available for questions, to find out how the kitty is doing, and to ascertain that they are observing the parameters you need diarized for evaluation. Let them know that it is unlikely that the initial dose will be the perfect one, and that, as they approach the "right" dose for this cat, there will initially be a marked reduction in urine output and drinking, however, after 3-4 days, these amounts will increase again as the cat's glucose homeostasis re-equilibrates.

The timeline for care that the author uses is:

- Diagnose diabetes mellitus by confirming with fructosamine; start insulin, diet and diary;
- 10-14 days later: in-clinic BG curve, adjust dose, teach ear prick BGs, add BID BG monitoring to diary for practice;
- Another 10-14 days later: in-clinic BG curve, fructosamine, adjust dose;
- Subsequent BG curves are performed at home, follow-up by email, phone or fax to adjust dose;
- Recheck cat q4-6 months (exam, fructosamine, U/A) as long as he/she is stable.

At the blood glucose (BG) curve appointment, hospitalize the cat with food and water, after weighing him/her and ascertaining what time the insulin was administered and what dose was given. Measure BG immediately, to get a starting level. Using a 25G needle works well, as a mere drop or two of blood are needed for the portable

glucometers. Plot the values on a graph for easier interpretation. Submit a serum fructosamine as well to determine how the average glycemic control has been over the past 10-20 days.

Continue measuring the BG every 1 (-1.5) hours over a 12-hour period. Ear sampling and a calm, reassuring manner will help to minimize the stress (and its associated BG elevations) somewhat. Nevertheless, the readings generally will be higher than what is occurring at home, therefore it is imperative to read the client's diary and take the clinical signs into consideration when adjusting the insulin dose. Once the blood glucose goes up for two consecutive measurements, the curve can be stopped. (Note this does NOT apply in the case of a cat in diabetic ketoacidosis.)

Use of the marginal ear vein is an accurate and easy technique for the measurement of BG. It is a useful technique in the clinic and, if the concept is introduced to clients with confidence and compassion, many are willing to perform curves at home. In general, these curves are more accurate as the cat's stress level is lower. Additionally, it is valuable for clients to be able to measure a spot glucose if their cat "doesn't look right" before deciding to give insulin or not.

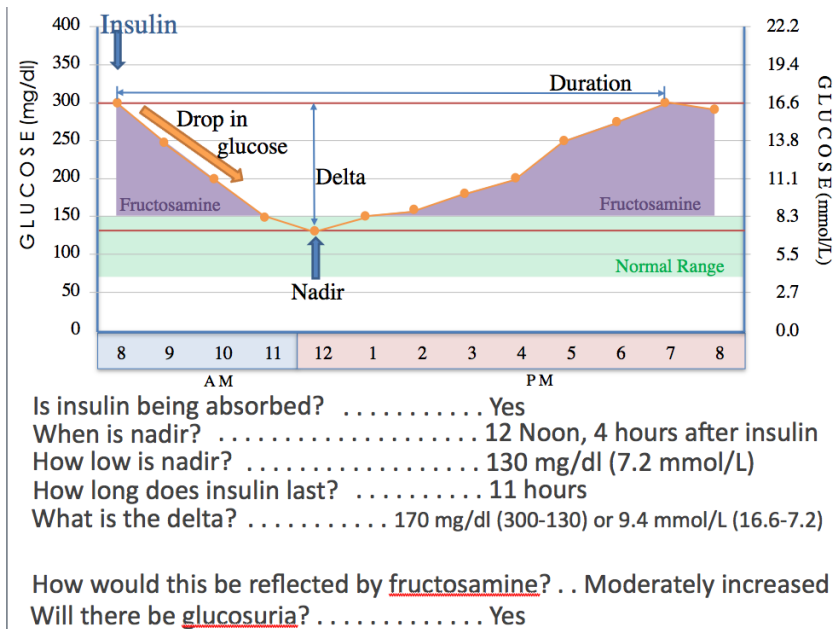
The goals of performing a BG curve are to determine (Figure)

- 1) Whether the insulin is being absorbed
- 2) The glucose nadir (level and time to reach it)
- 3) The duration of insulin effect
- 4) The degree (delta) of insulin effect, and
- 5) To assess the fluctuations of glucose levels in this individual patient!

When using glargine, the protocol for regulation and curving is somewhat different. The following recommendations come from Dr. Jacquie Rand:

- Measure glucoses every two hours for a minimum of 12 hours daily for the first three days in order to determine whether hypoglycemia is occurring as well as to assess how long the insulin is lasting in the individual. After this initial three-day period, dose adjustments are based on the pre-insulin BG (vs. nadir as with other types of insulin).
- If at a 7day hospital recheck, the pre-insulin BG concentration is > 290 mg/dl (16 mmol/L), increase the dose by 1.0 U/cat. A 12h curve should be done on the following day to make sure that hypoglycemia is not occurring at this increased dose.
- Do not change the dose if the pre-insulin BG concentration is 220-290 mg/dl (12-16 mmol/L).
- The dose should be decreased by 0.5-1.0 U/cat if the pre-insulin BG concentration is < 180 mg/dL (10 mmol/L). If biochemical hypoglycemia is present, the dose should be decreased by 1.0 U/cat. If clinical signs of hypoglycemia are present, the glargine dose should be decreased by 50%.

**Figure: Glucose curve parameters**



If a BG drops below normal range (< 80mg/dl or < 4.4 mmol/l), the staff person should notify the veterinarian after offering the cat some palatable food, as he/she may wish to administer dextrose intravenously to avoid a hypoglycemic crisis. Signs of hypoglycemia include weakness, lethargy, trembling, head tilt, ataxia, coma and death. If a hypoglycemic cat is offered food and doesn't eat right away, or if signs are severe, then corn syrup should be rubbed on the oral buccal mucosa while preparing to administer an intravenous dose of 50% dextrose.

The "Somogyi effect" is rebound hypoglycemia-induced hyperglycemia. If the cat's BG drops too low, the body reacts by releasing catecholamines (epinephrine), glucagon, glucocorticoids and growth hormone. This causes a rapid release of glucose into the serum causing this rebound to occur. It is important to not be tempted to increase the insulin dose in these individuals, as this would accentuate the problem and eventually cause a hypoglycemic crisis. "Spot checks" of BG levels should be avoided as they can be misleading and can mask a rebound effect and be misinterpreted as needing more insulin.

Over the next month or two, by performing blood glucose curves, measuring serum fructosamine and reassessing the cat clinically and historically (diary) every 2 weeks, the insulin dose suitable for this patient will be determined. Thereafter, it is advisable to see the stable diabetic cat every 4 - 6 months for a fructosamine. Consider, also, on these rechecks, to collect a sterile urine sample for urinalysis, as diabetic cats are more prone to bacterial urinary tract infections than non-diabetic individuals. If a diabetic patient becomes ill, then a glucose curve should be run as well as any other tests appropriate to their condition.

**UPDATE ON GLUCOMETERS:**

In a study comparing AlphaTRAK, Ascensia ELITE and reference hexokinase methods for determining serum glucose, the AlphaTRAK meter results did not differ from the reference method, however results from the Ascensia ELITE were significantly lower. The superior performance of the AlphaTRAK meter supports its use to monitor blood glucose levels in cats. (Zini, 2009)

Cats managed through home monitoring may have better glycemic control than those managed without (Reusch), however, whether in clinic or at home, there are limitations to sampling venous or capillary blood every 1-2 hours. Stress induces elevations of blood glucose making interpretation of the curve more difficult. Regardless of how diligent the protocol is, the nadir or peak effect may be missed. Since 2003, continuous glucose monitoring



systems (CGMS) /flash glucose monitoring systems (FGMS) have been used tentatively in veterinary medicine. (Davison 2003, Wiedmeyer 2003, Ristic 2005, Wiedmeyer 2008) These devices measure glucose concentrations in the subcutaneous interstitial fluid. Hydration status may influence accuracy with greater accuracy in better hydrated patients being suggested in a study of cats with diabetic ketoacidosis (Reinke, Medtronic MiniMed).

Several devices have been evaluated in animals including Medtronic MiniMed, Medtronic Guardian REAL-Time, iPro2 and FreeStyle Libre. One study showed that clinical accuracy appears to be better in the hyper- and euglycemic ranges than in the hypoglycemic range (Moretti with the Guardian REAL-Time, Coarradini in dogs with FreeStyle Libre). Moretti recommends checking the low normal values against a reference method. Some of the units need to have the recording device close to the cat while others do not, thereby allowing less restricted movement by the cat. Others require recalibration every 8-12 hours. There are numerous different sensors, some which can be used by the same system (Salesov). Placing the sensor on the dorsal neck provided glucose readings that were more accurate than placement of the same device on the lateral chest wall or in the knee fold (Hafner). In addition to use for home monitoring in the diabetic cat, there are several reports using CGMS to help regulating patients with diabetic ketoacidosis (Reinke: Medtronic MiniMed, Malerba: in dogs with FreeStyle Libre).

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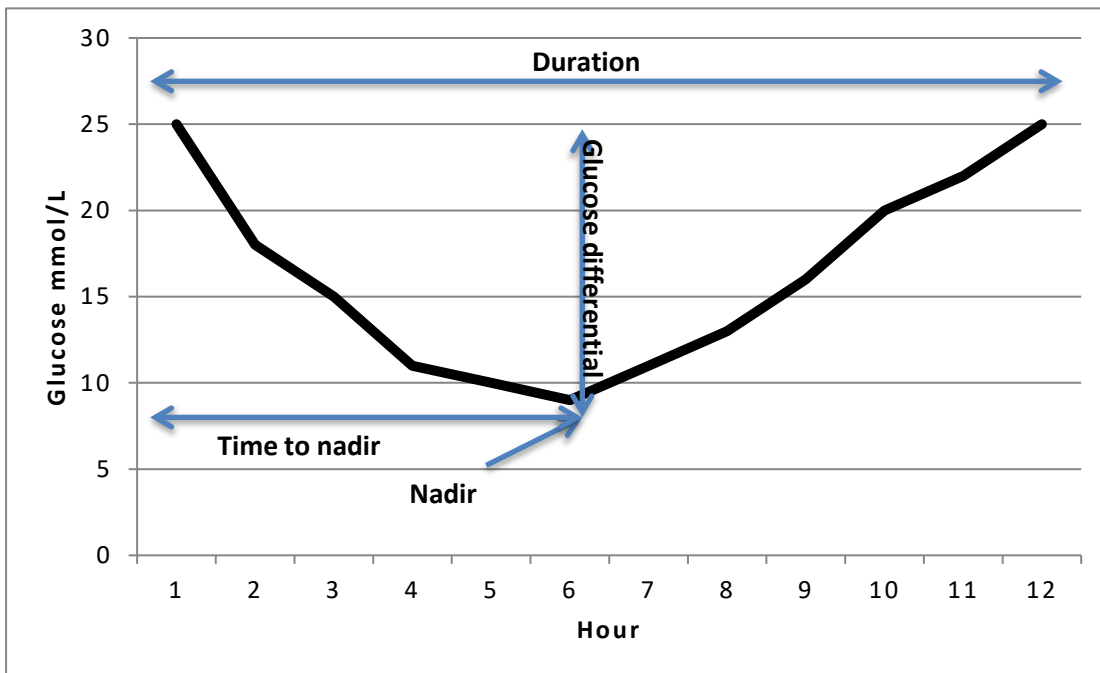
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**BLOOD GLUCOSE CURVES MADE EASY**  
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Blood glucose curves can be very helpful to determine the dose, frequency and type of insulin needed for a given cat. They are not difficult to interpret when simple rules are followed. It is very important to get a reading every hour. Cats should have food available at all times.

1. Start by looking at the shape of whole curve. Identify the nadir (lowest BG value), time to nadir, starting and highest BG value, duration (Figure 1).

Figure 1. Blood glucose curve elements



This graph is in mmol/L (convert to mg/dL by multiplying by 18)

Check if the blood glucose (BG) level decreases for a reasonable period of time. This indicates that cells see and respond to the insulin?

- If the curve merely wobbles around the starting level (e.g., curve D in Figure 2), then either:
  - The cells do not see/respond to this insulin;
  - The client is not administering the insulin correctly. This could be technique (intra-fur, intradermal resulting in poor absorption) or lack of comprehension (giving air, wrong dose);
  - The insulin is damaged (dropped, client wiped vial with alcohol, bacteria introduced into vial);
  - Counter-regulatory phase of Somogyi response to overdose.

2. Time between BG at time zero (just before insulin is given) to time at which BG level is the same = duration of action. This value tells you how long the insulin lasts in this individual.

- If duration is 9-12h, then BID administration is appropriate;
- If duration is 6-8h, then TID administration is appropriate.

3. Time to reach nadir indicates how rapidly insulin is being absorbed and taking effect. If peak insulin effect is between 2-4h after administration, be suspicious of Somogyi overswing (too much insulin). This will be followed by a rapid increase in BG with the curve exceeding the starting BG.

4. BG level at nadir indicates maximum effect of insulin.

IMPORTANT In order to determine nadir, one must have hourly BG readings. In fact, to really identify the nadir, we would need even more frequent readings, however with less than hourly measurements, we could easily miss a Somogyi, both at nadir as well as the overswing.

5. Glucose differential/delta is the difference between starting BG and nadir BG. If this difference is small (<7 mmol/L; 126 mg/dL), it is easy to decrease the starting BG without dropping the BG too low at nadir. This is a safe insulin to use for this patient. If the difference is large, it becomes difficult to increase the dose without risking hypoglycemia at peak effect.

6. Goal range for BG (not to be confused with differential) of 5.5-12 mmol/L; 100-215 mg/dL throughout the day provides good glycemic control and normalizes fructosamine levels.

Spot checking should only be done to determine whether a lethargic, wobbly cat is hypoglycemic (and needs glucose) or hyperglycemic (and needs insulin) before rushing the cat to the clinic. Using spot checks (i.e., anything less than hourly measurements) does not provide useful information and can result in making inappropriate recommendations.

Fructosamine reflects glycemic control, or time that BG is above ideal range over approximately the preceding 10-14 days. It is elevated if too little insulin is given but will also be elevated during Somogyi overswing, i.e., when too much insulin is being given. Glucosuria will occur under both situations as well.

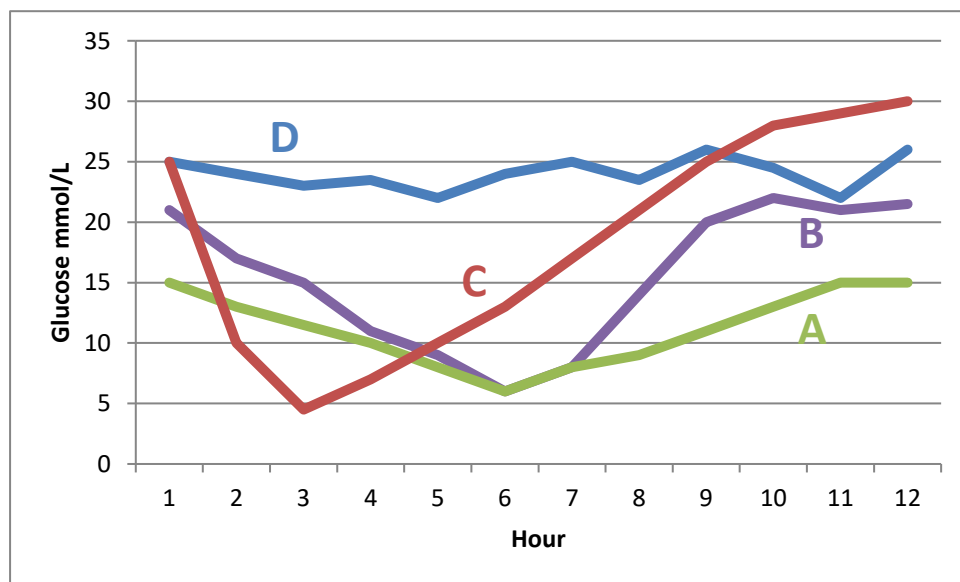
Figure 2. Examples of blood glucose curves

A Ideal curve => continue dose and type of insulin

B Short duration => give insulin more often or change type of insulin

C Somogyi overswing: rapid drop in glucose with counter-regulatory overcorrection => decrease insulin dose or change type of insulin

D Poor response due to client misunderstanding, poor technique, damaged insulin, attempt to correct from Somogyi response, extremely low dose => Client education, recheck curve. If no change, change insulin.



#### **USEFUL DIABETES RESOURCES**

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