

# Medical FAQs

## Managing Diabetes Mellitus in Cats

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### Introduction

Treatment and monitoring of diabetes mellitus (DM) in cats is a perpetually evolving topic. Some insulins have been discontinued over time, while newer treatments and monitoring methods have emerged. The VIN endocrinology consultants have summarized their opinions on therapy and monitoring of the diabetic cat below as of May, 2021. Diagnosing DM is discussed in various textbook chapters, journal articles, reviews, proceedings, etc. As such the reader is referred to those sources regarding diagnosis. For management of diabetic dogs, please see this [FAQ](#).

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### What owner considerations should be factored into a treatment strategy?

With endocrine diseases in cats, we seek to optimize patient quality of life and owner quality of life. It is important to keep these main goals in mind when devising a treatment strategy for a virgin diabetic cat. Here are some pointers:

1. **Make time to educate.** Provide ample time (**at least an hour**) for client education if this is the owner's first experience with a diabetic cat. Many owners have fears about not being able to board their pet because it has diabetes, or giving injections for example, or fear of causing hypoglycemia. Some owners want to know every detail regarding treatment while others just want to know what they need to do (injecting, diet, etc.). Educating and reassuring owners and helping them feel empowered are important aspects of successful long-term treatment. We cannot expect owners to remember everything straightaway and we should avoid information overload; consider planning several separate consults to cover the basics, involving the doctor and, if possible, the tech team to form a diabetes management team. Providing written information will help too.
2. **Weight loss and glycemic control.** For cats with DM, the importance of weight loss in overweight cats and of diet in any diabetic cat should be stressed, particularly for an owner 

would prefer to achieve diabetic remission in their cat. **Weight loss in overweight cats has been the only proven factor to significantly impact remission rates.** There is no evidence that so-called “tight regulation protocols” induce a higher rate of remission; instead, it could be that cats that are likely to achieve remission display tighter control even with a regular protocol. Additionally, tight regulation protocols have an inherently greater risk for hypoglycemia, thereby begging the question whether they are justified. If owners still want to pursue tight regulation, we have to ensure they do not go overboard with setting unrealistic and dangerous goals.

3. **Be realistic about cost and recognize financial restrictions.** Money spent on diagnostics could mean lack of money for treatment which could mean euthanasia of the diabetic cat. Monitoring can be intense with frequent assessment of blood or interstitial glucose to reduce risk of hypoglycemia, but will be inherently more expensive; offering alternative hands-off assessment using primarily clinical signs and cheaper ways of screening for risk for hypoglycemia will hand some clients and pets a (financial) lifeline and should always be discussed too.
4. **Give owners a realistic prognosis and cost estimate.** Let them know diabetic cats can do well and manage expectations early, including costs, expected number of visits and time to stabilization. Discuss the possibility of remission with appropriate management.
5. **Get a feel for management strategies early** (e.g., will we be able to employ continuous glucose monitoring [CGM] tools such as the Freestyle Libre, or will we be relying on single day glucose curves in addition to monitoring of clinical signs, weight stability, presence/absence of glucosuria etc.?) as this could help estimate time to stabilization and allow us to give a better estimate of initial costs.
6. **Cats are not people.** Many owners expect management to be similar to that of humans which is typically more aggressive and time-consuming. Compliance may be improved by realistically discussing with the owner what is possible and necessary and what is not.
7. **Get owners involved,** if possible, in management of their cat by using the [Royal Veterinary College Pet Diabetes App](#) available for Android and Apple smartphones. Also owners can be educated on the importance of monitoring clinical signs and calculating the “[Diabetic Clinical Score](#)” (DCS) of their cat which can dramatically influence treatment modifications and facilitate communication of their cat’s disease control with their veterinarian and veterinary technical staff.

## The Diabetic Clinical Score

Factor	Score
<b>Unintended Weight Loss</b>	0 = None, or gained since last examined 1 = Mild (<5% loss) 2 = Moderate (5-10% loss) 3 = Severe (>10% loss)
<b>Increased thirst &amp; urination</b>	0 = Normal 1 = Mild (Some increase noted by owner) 2 = Moderate (Increased filling of water bowl) 3 = Severe (constantly at bowl)
<b>Appetite</b>	0 = Normal or decreased appetite 1 = Mild polyphagia (finishes eagerly) 2 = Moderate polyphagia (finished eagerly and begs for more) 3 = Severe polyphagia (obsessed with food)
<b>Attitude/ activity</b>	0 = Normal 1 = Mild decrease (a bit less running and jumping) 2 = Moderate decrease (a lot less running and jumping) 3 = Severe decrease (lying about all the time)
<b>Total Score =</b>	<b>...out of 12</b>

8. **Encourage daily data gathering** by the owner to provide quality-of-life information that can easily be stored and evaluated through the Royal Veterinary College Pet Diabetes App. The app allows easy communication of all aspects of having a pet with diabetes and includes features

such as a diabetes diary function, medication reminder, DCS scoring, body condition scoring, caloric requirement calculator, and quality-of-life tools.

9. Have **information sheets** the owner can take home after their consultation as owners will not be able to take in all the information that they are told. Having trained, veterinary technical staff that can assist with client questions can benefit the client, primary veterinarian, and veterinary support staff as it can put the client at ease to know they have someone they can always reach out to in the future if/when they have questions.

## In general, what insulins are available now for maintenance of DM in cats?

Below is a general description of the various insulins currently available for use in companion animals.

1. **NPH insulins.** Humulin N® or Novolin N® (also marketed as ReliOn) are both NPH (Neutral Protamine Hagedorn) insulins, but anecdotal experience suggests their effect on blood glucose control is not equivalent. The VIN endocrinology consultants have observed many diabetic patients who were stable on Humulin N® but required a different dose of Novolin N® to manage their disease. In addition, Novolin N® can have a shorter duration of action making it unusable in a particular cat, while Humulin N® works fine. As such, one should not anticipate being able to make a 1:1 switch between the two products. These are both suspensions and therefore should be rocked gently (or rolled gently on a tabletop) several times to re-suspend insulin particles prior to withdrawing for administration (owners should be told **“Do NOT Shake”**). They are 100 U/ml insulin and therefore U-100 syringes should be used. NPH insulins **do not work well in many cats** due to short duration of action.
2. **Porcine lente insulins.** Vetsulin®/Caninsulin® is a 40 U/ml porcine Lente insulin preparation, and require U-40 insulin syringes. Vetsulin® is an FDA approved veterinary product (Vetsulin® and Caninsulin® are identical products with different brand names in different markets). Vetsulin®/Caninsulin® **does not work well in many cats** due to short duration of action. This insulin **should be vigorously shaken** before administering so as to achieve a milky consistency throughout the bottle prior to drawing up a dose. Vetsulin®/Caninsulin® is provided in convenient insulin pens which provides more precise dosing in ½ unit increments. Half-inch (12.7mm) insulin pen needles allow for easy dosing through the pen. Air bubbles should be removed prior to dispensing the insulin by discarding 1 unit into the sink. Additionally, the insulin is typically dispensed through the pen within approximately 5–7 seconds, so the needle should be held under the skin for at least that long; premature withdrawal after dispensing will lead to a lower dose being given. It is not uncommon for a drop of insulin to still be present at the tip of the needle following administration and removal from the skin. This is normal and does not mean that the patient was underdosed.
3. **Glargine and insulin detemir** are mainly 100 U/ml, clear aqueous solutions that are produced by recombinant DNA technology. Gently rocking the insulin bottle or pen several times prior to administration is recommended by the manufacturer despite these insulins being solutions. Lantus®, Basaglar®, and Semglee® are all 100 U/ml glargine products while Toujeo® is 300 U/ml. The higher concentration of Toujeo potentially makes it a better candidate for once-daily administration in cats (Saini *et al*, 2020). Glargine precipitates in the subcutaneous tissue, thereby allowing slower release of insulin over time. Glargine **cannot be diluted** with any solution. Detemir does not precipitate in tissue; instead, a fatty acid side chain, added to the insulin molecule, facilitates reversible binding to plasma proteins (particularly albumin), from where it is slowly released into the plasma. These formulations are also available in convenient dosing pens, but dosing increments are 1U rather than the ½ unit increments available with Vetsulin®/Caninsulin®. As with Vetsulin, the ½-inch (12.7mm) needles are effective for administration of insulin through the pen. Please note that many owners prefer a traditional syringe over an insulin pen and their preference should be the leading consideration in the process of electing the dispensing method. Using a pen is recommended whenever possible for small doses, as this can improve precision. Due to the high concentration, a pen **MUST** be used

with Toujeo. It is possible to draw the insulin out of the pen's insulin cartridge through the rubber seal with an insulin syringe. However, this increases the risk of contamination over time, as the rubber seal does not remain impervious to the environment after multiple needle sticks. Removing insulin from the pen with a syringe should only be necessary when needing to give ½ unit doses. Whenever possible, when using an insulin pen, dispense the insulin directly from/through the pen.

4. **Prozinc®** is a human recombinant insulin that is precipitated with zinc and is stable in suspension. It only requires **gentle rolling to mix** prior to administration. It is formulated at a concentration of 40 U/ml. Therefore, appropriate U-40 syringes should be used. It is also approved for veterinary use by the FDA and **is a good initial insulin in cats**.
5. **Insulin degludec**. Tresiba® (insulin degludec) is a recent entry into the veterinary medical field. Very little information is known on its use in cats (Oda *et al*, 2020). Similar to detemir, it has a fatty acid side chain added and is a solution rather than a suspension. It forms hexamers following injection. Due to its characteristics, it may have more predictable absorption and less day-to-day variation, and is administered through an insulin pen. Despite this insulin type being used less than once daily in humans with a duration of action of 40 hours, data thus far suggests it does need to be used at least every 24 hours in cats.

Most clinicians **prefer to start insulin therapy every 12 hours** as most cats require it for good control and it may increase the chance of remission. An optimum location to administer insulin for injection may be along the lateral abdomen and thorax. The dorsal neck or scruff has commonly been used as a site for injection, but this site may be less than ideal in some patients due to low blood flow and increased fibrosis caused by repeated, historical injections in that area. Moving each subsequent injection to a different site each time is recommended.

**Insulin pens** can minimize daily blood glucose variability by maximizing precision of administration of the insulin dose, particularly with small doses. One paper concluded that lower doses of Vetsulin® (less than or equal to 2 units) are more accurately dosed with a pen versus a syringe. Higher doses were more accurate using U-40 syringes (8 and 16 unit doses) (Malerba *et al*, 2021). Pens can be stored in the refrigerator to prolong their potency. Most VIN consultants recommend that an insulin (whether it be pen or bottle) can continue to be used, if refrigerated, for up to 3–4 months as long as the insulin remains free of any contaminants, or discoloration (NOTE: most inserts state the insulin should be discarded 28 days after first use).

For **any cat that needs a small amount** of 100 U/ml insulin, use 0.3 ml or 0.5 ml “low-dose” syringes for accurate dosing when drawing insulin from a bottle. The scale on the syringe is easier to read for small doses. Larger volume syringes can be more difficult to read and a small error can have big consequences when a patient requires a very small dose to begin with. Magnifiers for syringes can also be used for owners with sight difficulties.

### What insulins are preferred in cats?

**Glargine** 100 U/ml products, **detemir**, and **Prozinc®** are the most popular insulins for use in a virgin diabetic cat, with most veterinarians reaching for 100 U/ml glargine when possible or 40 U/ml Prozinc®. **Toujeo®** (glargine 300 U/ml) is an option for cats who experience high daily variability in blood glucose concentrations when receiving one of the other insulin products. Note that Toujeo **MUST** be given using the insulin pen in which it is distributed, and the pen only allows one-unit increments for dosing. So, if you are a clinician that likes to be able to dose in ½-unit increments, you may elect to avoid using this product. Expense precludes its use routinely for many cats. Glargine and detemir are solutions, so gentle mixing prior to administration is all that is required.

1. Prozinc® is distributed in a vial and requires U-40 syringes. Toujeo® is only available via an insulin pen.



2. Glargine 100 U/ml products are available in pens and vials as is detemir.
  - a. Currently in the United States, Semglee® pens and the 10ml vials are about ½ the price of Lantus pens and 10ml vials.
  - b. Basaglar® only comes in 3ml pens and they are about two-thirds the price of Lantus® pens.
3. A **simplified dosing scheme** versus calculating a specific u/kg dose is to administer 1 unit per cat q12hr for an average-size cat or 2 units per cat q12hr for a big cat.
4. After starting insulin, the cat is sent home and the dose remains unaltered until re-evaluation (at home or in-clinic) 7 days later. The dose is only altered earlier than 7 days should hypoglycemia be suspected or documented.
5. Toujeo® can be administered with an insulin dosing pen at a starting dose of 0.5 U/kg q12h (Linari *et al*, 2020).

Some cats can be managed well with Vetsulin®/Caninsulin®. Vetsulin® is an FDA-approved veterinary insulin; yet, duration of action can be too short in a large proportion of diabetic cats.

Therefore, the VIN endocrinology consultants **do not routinely recommend**

**Vetsulin®/Caninsulin®** insulin as an initial insulin for cats. These should be reserved for situations where alternatives have failed previously or are not (legally) available or financial constraints allow for Vetsulin®/Caninsulin® use only. They may be easier to dose due to a smaller volume needed in cats and lower concentration (40 U/ml).

*In general, no single insulin is suitable for ALL diabetic cats. If you successfully stabilize most of your cats on a given insulin type, keep using it!*

### How soon do I recheck a cat after starting insulin?

After starting insulin, cats are sent home and the dose remains unaltered until re-evaluation (at home or in-clinic) 7–14 days later. The dose is only altered earlier than 7 days should hypoglycemia be suspected or documented.

### How important is diet in managing my diabetic cat?

Feeding a suitable diet is an essential part of treatment of feline diabetics (Gostelow *et al*, 2014). In overweight/obese cats, weight loss should be an important target; this increases insulin sensitivity, aids improvement of glycemic control and increases the chance of obtaining diabetic remission. The following guidelines should be considered when choosing a diet for a feline diabetic:

- The diet has to be palatable to ensure consistency in day-to-day caloric intake
- Carbohydrate content should be as low as the cat will eat. Some recommend a carb content of 12-15% of metabolizable energy (ME) with protein content <sup>3</sup> 40-45% ME (low carbohydrate, high protein diet). A carb content as low as < 7% ME has been recommended by others (Zoran and Rand, 2013; Sparkes *et al*, 2015). The VIN endocrinology consultants endorse the <7% recommendation; this is only achieved by feeding a wet (i.e., not dry) low carbohydrate diet.
- Wet food is preferred to kibble as the carbohydrate content is usually lower.
- If another medical condition requiring dietary therapy is present, it often should take priority over the diabetic diet. The number of calories needed should be calculated based on estimated optimal body weight. See [VIN energy calculator](#). This is only a guide and may need to be adjusted based on regular weight checks (initially once a week).
- If weight loss is attempted, it should ideally be 0.5–1.0% of the bodyweight/week. Strategies to increase overall physical activity may be required. Weight loss can lead to increasing the chance for diabetic remission 13-fold.



- Optimal frequency of feeding has not been established. Grazing cats can continue to graze, as long as their daily caloric intake is held consistent and they do not gain weight beyond what is perceived to be their optimum weight. Cats that DO NOT graze should be fed in alignment with insulin administration.

*The VIN endocrinology consultants strongly recommend feeding an all-canned diet that is less than 7% ME or as low in carbohydrates as the cat will eat. For example, one option is the canned Purina DM (<7% carbs ME). There is a ‘Savory Selects’ line of canned DM that is higher in carbs and as such is NOT recommended. The **Protein/Fat/Carb/Phosphorus** chart at [www.catinfo.org](http://www.catinfo.org) lists many of the over-the-counter canned foods in the United States. Look for the brands/flavors that are <7% carbs ME. This chart is written on a ‘calorie %’ basis which is the SAME as the ‘ME’ or ‘energy’ basis. DO NOT compare to the ‘dry matter’ or ‘as fed’ basis on the label of the can.*

## How likely is remission in my diabetic cat?

Many diabetic cats can achieve remission, but no single test can predict the occurrence of remission in an individual cat. A remission rate of 30-40% of newly diagnosed diabetic cats is realistic; remission is most common in the first 6 months after diagnosis and becomes less likely thereafter. Treatment with longer acting insulin preparations and a low carbohydrate, high protein diet to promote weight loss and resolve obesity correlate with higher remission rates. Achieving good glycemic control early in the course of the disease may also increase the chance of remission; on the other hand, achieving good control early may be more likely in cats that will go into remission, i.e. be the effect of being able to go into remission and not the cause of the remission.

Despite their popularity, there is currently **no evidence that tight control protocols** that dose insulin to achieve complete euglycemia are superior to traditional approaches, which aim for a safe nadir and control of clinical signs (Gostelow *et al*, 2014). If clients are “super” motivated to aim for euglycemia, tight control protocols could be considered (provided the clients have been advised of the lacking evidence). Use of intense protocols must include frequent home blood glucose monitoring and/or use of continuous glucose monitoring devices, in order to be safe.

**Weight loss is independently associated with remission.** Weight loss strategies, if a cat is overweight, should dominate the management protocol.

Cats that achieve remission have persistently impaired  $\beta$ -cell function and should be continued on a low carbohydrate, high protein diet lifelong. About 30% of cats that achieve remission will relapse and need insulin treatment to be reinstated (Gottlieb *et al*, 2015). Therefore, monitoring of the cat for re-occurrence of clinical signs and re-assessment if these re-occur are strongly advised.

If **hypersomatotropism/acromegaly** (which causes the diabetes mellitus in up to 1 of 4 diabetic cats) is present, permanent remission is unlikely. Screening for hypersomatotropism by measuring serum IGF-1 concentrations is reasonable if a cat is insulin-resistant, as proven by continuous glucose monitoring, or experiences weight gain despite poor blood glucose control.

## What are treatment goals and recommended monitoring strategies?

The main treatment goals in cats with diabetes mellitus are to **resolve clinical signs, avoid hypoglycemia, and improve quality of life of the cat and owner.** The VIN endocrinology consultants encourage all colleagues to bear this in mind. All too often it proves too tempting to be chasing beautiful blood or interstitial glucose numbers despite there already being a good clinical picture.



The main treatment goals can often be achieved by lowering blood glucose, whilst ensuring it never drops so low that hypoglycemia occurs or becomes likely. Older recommendations suggest specific glucose concentration numbers as a guide. This is, however, probably not helpful for a variety of reasons. Firstly, the clinical picture should drive the assessment, not these numbers. If there are no clinical signs of diabetes mellitus, we look at serial glucose data to see whether there is a risk for or occurrence of hypoglycemia; if that is not the case, we have achieved our aim, and there is usually no need to make the numbers more perfect. If clinical signs persist, we use serial glucose data to see how to improve control. If the nadir (lowest point of the blood glucose series) indicates we can increase the insulin dose safely (i.e., nadir > 100 mg/dl or 5.0 mmol/l), we do so. If the nadir does not allow this, we need to seek alternative measures to lower overall glucose concentrations (e.g., use insulin with a longer duration of action if one is available or increase the frequency of administration to BID if giving once daily).

As stated above, some diabetic cats enter a state of diabetic remission with exogenous insulin no longer being required. Not every cat achieves remission, yet it is likely feasible in approximately 30-40% of cats (Zini *et al*, 2010). Treatment of an underlying disease (e.g., acromegaly/hypersomatotropism in cats, obesity) should be undertaken when possible, as its resolution or control might result in remission of the diabetes.

Many monitoring protocols can be found throughout the veterinary and lay literature. One protocol will not be the right answer for all cat/owner combinations. It is more appropriate to adhere to monitoring principles, underpinned by knowledge of advantages and disadvantages of each tool. The right strategy will be different for each cat/owner combination and may change over time for that same combination. Some owners will benefit from a more intense protocol when trying to avoid hypoglycemia at all costs. Others may be motivated by maximizing the chances of diabetic remission for their cat (but note that a recipe for this does not exist). Some may wish to adopt a more pragmatic approach with less intense management. Regardless, monitoring needs to be tailored to a specific cat/owner combination and the veterinarian's utilization and comfort with the monitoring tools. The goal in this section moving forward is to briefly discuss these tools in addition to pros and cons so each clinician is familiar with them and can implement them with their particular cases.

Initially, re-assessment of a diabetic cat is recommended using the most appropriate tool(s) for the specific cat/owner every 7-14 days. On each occasion, insulin dose can be increased, decreased or left unchanged depending on data obtained by assessment of the clinical picture and glycemic monitoring parameters. In general, the insulin dose should not be changed more frequently than every 7 days unless decisions are being guided by a CGM like the Freestyle Libre or moderate to severe biochemical hypoglycemia or any level of clinical hypoglycemia is seen. In some instances when using a CGM, we can adjust doses more frequently than every 7 days. Follow-up reassessment is recommended after any change to therapy.

### 1. Clinical signs, diabetic clinical score (DCS), body weight/condition score

- a. Assessment of the clinical picture along with the DCS should always precede evaluation of any glycemic parameter, and the two should be interpreted concurrently to make necessary adjustments. See the [DCS sheet](#).
- b. The RVC Pet Diabetes App features many functions, including the ability to perform a DCS prior to a cat's visit enabling easy communication of many aspects of having a cat with diabetes.
- c. The clinical picture tells us the truth about whether there is consistent hyperglycemia (unless the owner is unobservant) and is cheap, and a validated scoring system is available. Weight stability, reduction/control of polyuria/polydipsia (PU/PD), and presence/absence of glucose in the urine can all be factored into the decision-making process of whether an adjustment in insulin is required.
- d. The disadvantage is that the quality is owner- and clinician-dependent, so inherent subjectiveness in this score exists.



- e. If a cat is maintaining weight, not showing excessive thirst, eating with a normal appetite and is generally considered to be well, then frequent follow-up is not likely necessary. In such cases, our main aim is to screen for risk for hypoglycemia (since these cases may not necessarily show any clinical signs). The clinical picture should hold more weight than a single glycemic monitoring parameter due to pitfalls associated with all of them (blood glucose curves, Freestyle Libre, fructosamine, spot blood glucose test, urine glucose/ketone assessment). The exception is documented moderate to severe hypoglycemia when the dose must be decreased.

## 2. Blood glucose curves (BGC)

- a. Although controversial and far from perfect, BGC, together with the continuous interstitial glucose monitoring devices, are the only techniques that have the ability to determine causes for poor control, have the potential to reflect an approximate blood glucose nadir and can reflect the amount of time the blood glucose remains under the influence of injected insulin (insulin duration of action).
- b. **A main limitation that should be borne in mind is the natural day-to-day variation in glucose profiles. Even when we do not change anything, a curve on Monday will be different than what is seen on Tuesday, Wednesday, etc. Therefore, the VIN Endocrinology consultants recommend against checking spot glucoses at the time of the nadir on a previous BGC; the nadir occurs at a different time each day.**
- c. **Ideally, BGC are performed in the home environment; most, but not all, owners can be taught to do this.**
- d. The strict control of BG required in diabetic humans is not practical nor proven necessary in veterinary patients. Strict control in humans is required to avoid more dangerous complications such as nephropathy, neuropathy, retinopathy, and vasculopathy that, for whatever reasons, are not prevalent in veterinary populations.
- e. A phenomenon exists in human diabetics referred to as “hypoglycemic unawareness”. In this situation, the body does not respond to mild or even moderate hypoglycemia and clinical signs do not develop. However, when severe hypoglycemia occurs, profound clinical signs appear acutely without warning. Although unproven, some believe the same occurs in veterinary patients. A glucose curve will hopefully document mild hypoglycemia that can be fixed before a seizure occurs. Thus, periodic curves can help even in a seemingly well-controlled patient.
- f. Other techniques and clinical signs can suggest that control is lacking, but multiple reasons for poor control including too low and too high a dose of insulin exist. The only way to know how to change therapy to gain control is by performance of a curve, or better, a series of curves or continuous glucose monitoring in the home situation.
- g. For a glucometer, the VIN endocrinology consultants prefer the AlphaTRAK 2.
- h. Blood glucose concentrations are measured in general, every 2 hours for one interval between injections (i.e., for 10–12 hours) when insulin is administered q 12h. When the BG is <150mg/dl (8.3mmol/L) the concentration should be measured hourly. A normal insulin/feeding schedule MUST be maintained as much as possible. The curve should be cancelled if the pet does not eat normally the day of the curve. The pet should be fed its standard diet at the usual time and insulin given by the owner preferably at home as many pets refuse to eat if we try to obtain a blood glucose concentration prior to administering insulin in the hospital. We would prefer a cat eat normally than worry about a pre-insulin blood glucose concentration and feeding at home ensures this more routinely.
- i. It is the clinician’s hope that the curve will establish the nadir and duration of effect. Remember that the nadir and apparent duration can vary between curves (Fleeman et al, 2003). This emphasizes the need to interpret BGC data in light of the patient’s clinical signs. A cat could have a curve several days in succession, and a different decision could be reached depending on the day of the curve. This has become less of a problem with the advent of the Freestyle Libre flash glucose monitoring system described below.
- j. **Hypoglycemia should always be avoided.** No matter what the BG concentrations are during the day, if the nadir is below 80mg/dl or 4.4mmol/L, a modest reduction (e.g., 1 

units) in insulin is reasonable if no signs of hypoglycemia are present. A more radical reduction (e.g., 50%) is needed if signs are present.

The Somogyi phenomenon, also called hypoglycemia-induced hyperglycemia, refers to hypoglycemia followed by marked hyperglycemia. It results from a normal physiological response when BG declines to <60 mg/dL (3.3mmol/L) or when BG concentration decreases rapidly regardless of the nadir. In either case, a number of reflexes are triggered that act to increase BG. Counter-regulatory hormones such as epinephrine, cortisol, and glucagon are secreted, and the resultant hyperglycemia usually occurs rapidly, with BG's of up to 400–800 mg/dL (22.2–44.4mmol/L). If the Somogyi phenomenon occurs, insulin dosage should be decreased so the nadir is >80 mg/dL (4.4mmol/L); counter-regulatory hormones will no longer interfere with the action of the exogenous insulin and true duration of effect will become apparent. If the duration of insulin action is truly < 8 hrs, adequate therapy with that type of insulin requires injections more frequently than twice daily, which is impractical for most owners. A different kind of insulin should be tried.

a. Disadvantages of BGC include the fact that they can be expensive to perform, they are susceptible to stress, especially in cats, and biologic day-to-day variation in BG concentrations can result in misjudgements being made in required insulin adjustments. If they cannot be performed at home, they often do not truly represent the animal's routine.

k. If the clinical picture does not match the curve, suspect the curve.

### 3. **Freestyle Libre flash glucose monitoring system**

- a. This has now become the reference standard serial glucose monitoring tool. The Freestyle Libre flash glucose monitoring system is a continuous glucose monitoring system that can be purchased online or through a local pharmacy with a prescription. It can obtain glucose data in the home environment without the stress of regular blood sampling.
- b. The system contains a small sensor that is placed on the patient's skin; attached to the sensor is a small needle that goes through the skin into the interstitial space, and it continuously transmits interstitial glucose data that can be measured by a handheld reader or newer smartphone applications.
- c. As it is a continuous glucose monitoring system, interstitial glucose concentrations are recorded un-interrupted for up to 14 days, as long as the sensor remains functional and attached to the diabetic patient. Such data provide information to the clinician on daily variability of blood glucose concentrations and provide objective BG data over an extended period of time.
- d. An [extensive FAQ](#) is available discussing how to obtain and apply it to the cat. The FAQ will familiarize you and the client with the software and equipment. [This discussion](#) from the VIN message boards also discusses how to upload data from the sensor and reader to the Libreview software. The software analyzes the data from the device and displays the information on your desktop computer..
- e. If the clinical picture does not match the data, suspect the data. For example, if the Libre sensor is reading <75mg/dl (<4.2mmol/L), the reader will suggest double-checking this value with a glucometer, as it may not be correct. In the data that Abbott collected to bring the Libre to the market, approximately 40% of the sensor readings in humans of glucose levels <75mg/dl were in error.

### 4. **Serum fructosamine concentration**

- a. Serum fructosamine (glycosylated albumin primarily) reflects the average glycemic control over the previous 1-3 weeks. It forms at a rate proportional to the average BG present (i.e., the higher the mean BG concentration over time, the greater the concentration of fructosamine).
- b. Advantages include the fact that it requires only a single blood sample, is not affected by stress, which is useful in cats, and is a much smaller investment in time and money than a glucose curve.



- c. Disadvantages are that it provides no detailed information about the nadir and may not identify a risk of hypoglycemia. It can be elevated from too little insulin and also when the pet receives too much insulin and suffers from bouts of hypoglycemia-induced hyperglycemia.
- d. Increased utility may best be through assessment in trends from recheck to recheck over time.
- e. Remember that the reference interval for fructosamine is for non-diabetic patients. Diabetic animals typically have periods of hyperglycemia and, thus, a fructosamine value above the reference interval. It is recommended to aim for a concentration slightly above your laboratory's reference range. A fructosamine that is in the lower part of the reference range or below could indicate chronic hypoglycemia.
- f. The fructosamine assay can be unreliable. If the clinical picture is great and the fructosamine not so, believe the clinical picture. Laboratory results can vary greatly across different facilities and even more so with in-house testing, so isolated fructosamine values are likely of little use. Monitoring of trends over time may be more useful. One source considers 50umol/L to be the so-called critical difference (i.e. the difference between two consecutive fructosamine measurements has to exceed 50umol/L to reflect a change in glycemic control) (Reusch, 2013). A second publication reports the critical difference as 33umol/L (Link *et al*, 2008).

#### 5. **Spot blood glucose concentration**

- a. As the name implies, this is a single blood glucose determination.
- b. As such it is cheap, minimally time-consuming, and easy to perform.
- c. If the concentration is low, insulin overdosing is possible or the cat may be in diabetic remission. Consideration should be given to reducing the insulin dose or, perhaps, discontinuing the insulin. If there are no clinical signs of hypoglycemia, a low BG should be verified before a change in dose is made.
- d. A single reading provides no info as to whether the insulin dose should be increased, can be affected by stress and cannot provide information on nadirs or duration of action (since the nadir will be at a different time each day).

#### 6. **Urine glucose/ketone concentrations**

- a. Both are easy and cheap to perform and can be measured at home
- b. Continued absence of glucose in the urine most times implies **excessive** insulin dosages and/or remission in cats and should prompt performance of BGC or use of a Libre to assess the insulin dose.
- c. Uniformly elevated urine glucose readings coupled with poor clinical control suggests the insulin regimen is inadequate. As with persistently negative urine glucose, further case review is warranted; insulin dose increases are not recommended based solely on urine tests alone.
- d. As urine glucose can be measured at home it can be a helpful parameter to assess in cats that have stress hyperglycemia in the hospital.
- e. It is expected that stable diabetics will typically have some glucose in their urine during each day.
- f. Ketones can sometimes be present in well-controlled diabetic pets. A small amount of ketones in a patient that feels well may not be a problem. Moderate to large amounts of ketones should be a trigger for further evaluation whether or not the patient is feeling well. Any ketones in the presence of an unwell patient should be investigated.
- g. Note that the nitroprusside reaction used in urine dipsticks for detection of ketone bodies detects acetoacetic acid and acetone but not beta-hydroxybutyric acid. Shock-like states (severe DKA) promote production of beta-hydroxybutyric acid. After insulin treatment, this is metabolized to acetoacetate, and, hence, some animals will initially be ketone-negative but become ketone-positive after 2-3 days of treatment despite clinical improvement.

**I can't seem to regulate my diabetic cat – is my cat insulin-resistant?**



Insulin resistance should be suspected in any cat in which marked hyperglycemia persists throughout the day despite insulin doses of >1.5U/kg per injection being required to maintain adequate glycemic control. However, this does not absolutely mean insulin resistance is present. The problem could lie with owner/patient management issues or insulin choice. Lack of response to high doses of one insulin type does not mean all insulins will be ineffective. So initially, before pursuing a costly workup for insulin-antagonistic diseases, factors that mimic insulin resistance should be excluded.

1. Owner technique and insulin handling should always be evaluated.
  - a. If using Vetsulin®, are owners shaking the insulin thoroughly? If using NPH or ProZinc insulins, are they gently agitating the suspension?
  - b. Are the correct syringes U-40 versus U-100 being used for the insulin type?
  - c. Can the owners draw up a proper dose and can they properly read the syringe?
  - d. Do the owners move injection sites around with each dose? Are they injecting over the flank or lateral thorax, as preferred?
  - e. If using pens, are they dispensing a unit or two into the air to confirm the pen is functioning properly? Are they holding the needle under the skin for at least 5 seconds?
  - f. Are they using a long enough insulin pen needle (1/2 inch or 12.7mm) to get through the skin?
2. Is the owner feeding a canned, low carbohydrate/high protein diet when possible? Is the owner feeding the correct number of calories each meal or per day? Is it the SAME number of calories each day or, if meal-fed, each time? Cats can either be fed twice-a-day OR can graze on their food throughout the day, but the TOTAL amount each day should be the SAME each day and should be an appropriate number of calories to maintain the cat at the ideal body weight (avoiding/correcting obesity).
3. If an owner issue is suspected, a glucose curve or Freestyle Libre can be performed after the owner is observed preparing, withdrawing, and administering insulin with a new bottle or pen of insulin.
4. Impostors of resistance should be assessed. Curves should be evaluated for marked post-prandial blood glucose surges; if these are noted, a change in timing of insulin administration may solve the problem if the cat is meal-fed. Other impostors are the Somogyi phenomenon and inadequate duration of insulin action.
5. Pathologic causes for insulin resistance can be considered if management issues are excluded.

In cats, genetic and acquired factors (such as abdominal fat and lack of exercise) act together to produce insulin resistance and impaired glucose tolerance, producing hyperglycemia despite hyperinsulinemia. Hyperglycemia then causes glucose toxicity, which causes pancreatic beta-cell failure and, paradoxically, reduced insulin secretion. Eventually, over days to months, if continued, diabetes mellitus ensues.

Understanding the pathophysiology in cats allows identification of some specific treatment goals, because it IS possible to improve the diabetic condition by addressing some of these factors. Goals should include reducing abdominal fat (weight loss) and increasing activity, when possible, in addition to treating the DM with insulin to remove the hyperglycemia that is suppressing the beta cells. DM in cats, as mentioned previously, might be reversible if treatment is started quickly and effectively. Similar to dogs, iatrogenic DM occurs secondary to exogenous drug administration such as glucocorticoids and progestogens as well as to pancreatitis. Although more rare, feline Cushing's disease also can result in development of DM. Assessment of oral health should be performed, as infection there and in the urinary tract may result in insulin resistance.

It is important to be aware of the possibility of acromegaly (hypersomatotropism) in cats, as affected cats have a specific cause for their DM. Not all cats with acromegaly show obvious phenotypical signs such as a broadening of the face, increased interdental spaces or large feet. Screening is relatively easy, needing only a serum IGF-1 concentration. A diagnosis is a game changer in terms of prognosis



and expectations. Where available, acromegaly can be treated by hypophysectomy, thereby curing the acromegaly and resulting in diabetic remission in some cats or, at least, reduction in the amount of insulin required. Radiation therapy is also possible, yet not a cure.

*When a cause for insulin resistance is sought, the easiest causes to rule out and the most likely should be eliminated first, proceeding through to the least likely. The following order, in general, has been recommended in cats: concurrent drugs, obesity, acromegaly, concurrent disease (including infection and ketoacidosis), hyperthyroidism, and hyperadrenocorticism. If strong evidence exists for a differential diagnosis lower in the order, that possibility should be ruled out first.*

### **How do I deal with hypoglycemia in a diabetic cat?**

One dilemma can be when we see hypoglycemia despite apparently low doses of insulin. As always, the owner is suspect, and technique should be reviewed, if at all in question. Remember that once a cat becomes hypoglycemic on insulin, it can take up to 3 days off therapy for the diabetes to return, if it does. Continued euglycemia after resolution of hypoglycemia means the cat has gone into remission. Differentials to consider for hypoglycemia are:

- use of an incorrect syringe (U-40 versus U-100)
- concentrated insulin, i.e., improper mixing
- overlap of insulin action, e.g., sometimes the duration of action can be longer than 12 hours in a patient resulting in the BG still falling as the time for the evening insulin dose arrives. If the same dose is again injected, this can create an overdose at night and subsequent hypoglycemia-induced hyperglycemia the following morning.
- anorexia
- emesis
- maldigestion/malabsorption
- transient diabetes
- too high an insulin dose

In cats, if the insulin is being given correctly and the cat becomes hypoglycemic on a very low dose of insulin, the first thought should be that the diabetes is in remission and insulin is no longer needed. Another consideration is some type of malabsorptive disorder, e.g., IBD.

### ***Are incretins useful for managing diabetic cats?***

The amount of insulin that is secreted in response to an oral glucose load is higher than the amount secreted in response to the same load given IV. The difference in amount is called “the incretin effect”. Incretins are gastrointestinal hormones secreted by enteroendocrine cells in response to eating nutrients such as glucose and fatty acids. The 2 main incretins are glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). They are broken down by the enzyme dipeptidyl peptidase-4 (DPP-4). Besides increasing insulin secretion, GLP-1 also decreases glucagon secretion, stimulates beta-cell differentiation, delays gastric emptying, and induces satiety.

Pharmacological manipulation of incretins comes through use of either GLP-1 mimetics or DPP-4 inhibitors, which augment the effect of endogenous incretins. Incretins have been used to help treat diabetes in humans or as weight loss aids.

Some evidence exists for their use in veterinary medicine. Incretins may be more helpful in diabetic cats as cats are mainly Type II diabetics, and, at least in the early stage of diabetes, most cats retain insulin secretory ability. In diabetic dogs, the actions of causing beta-cell differentiation and decreasing glucagon secretion (glucagon is a major insulin antagonist) may be of some help. Incretins would be

used in concert with insulin, not as a substitute. Non-extended release exenatide (Byetta®) was found to be safe and potentially decreased insulin dose and improved weight loss (Scuderi *et al*, 2018). On the other hand, a long-acting GLP-1 analogue exenatide (trade name Bydureon®) improved the remission rate and percentage of cats that achieved good control, but, potentially due to the study being underpowered, the difference was not significant (Riederer *et al*, 2016). For cats on insulin and exenatide ER (EER), 40% went into remission and 89% achieved good control as compared to 20% and 58%, respectively, for cats on insulin and a placebo. On the other hand, a more recent study with the same product found that the combination of EER, insulin, and a low carbohydrate diet might be advantageous in the treatment of newly diagnosed diabetic cats (Kramer *et al*, 2020).

### ***Can I use oral hypoglycemic agents?***

No veterinary licensed oral hypoglycemic agents are available. These agents provide sufficient glycemic control in a minority of cats as sole therapies and are not recommended as first line treatment (Gostelow *et al*, 2014). They could be considered if a cat owner absolutely refuses to administer insulin or is unable to inject insulin. Glipizide is the drug in this class most often used. Protocols for use can be found in veterinary textbooks.

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